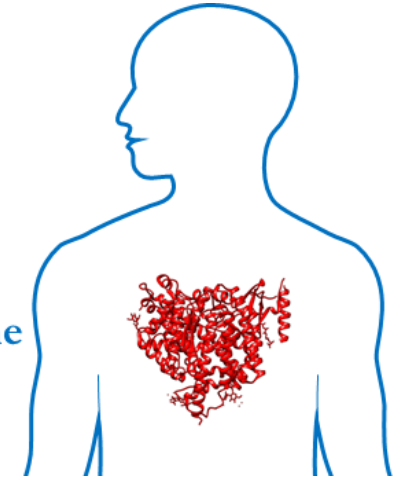
BAM
Biologically Active Metallopeptides

MRTBS 2024
I Międzynarodowa Konferencja
Nowoczesne trendy badawcze w naukach biomedycznych: holistyczne ujęcie opieki zdrowotnej.
Opole, Polska, 17-19.04.2024



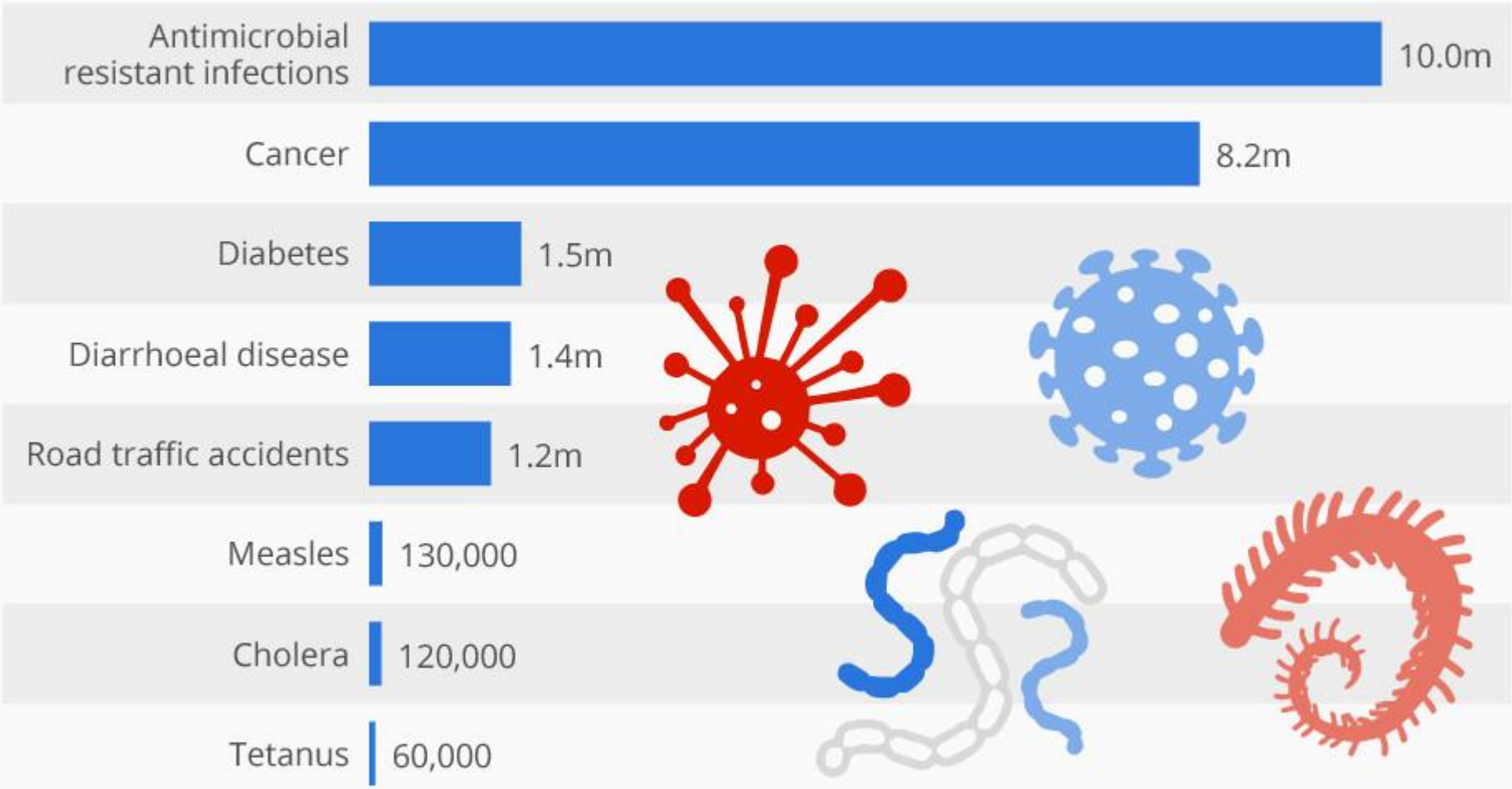
Metal ions – the eminence grise of antimicrobial peptides?

Magda Rowińska-Żyrek

Uniwersytet Wrocławski

Deaths From Drug-Resistant Infections Set To Skyrocket

Deaths from antimicrobial resistant infections and other causes in 2050

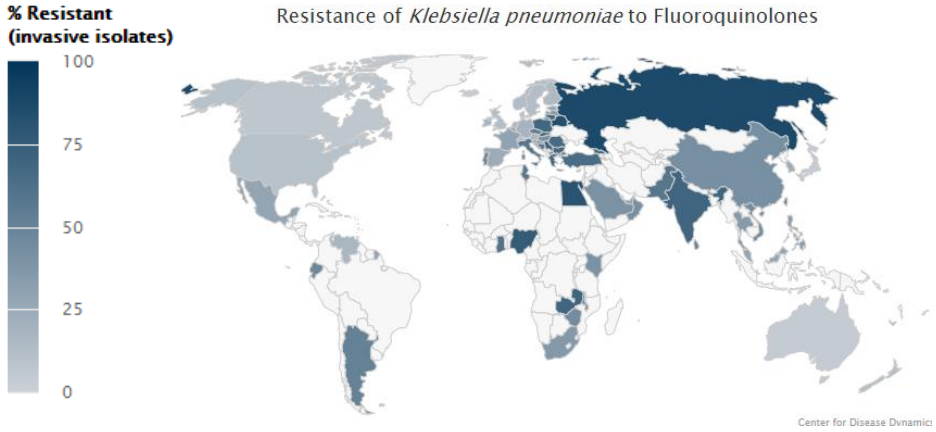


Source: Review on Antimicrobial Resistance

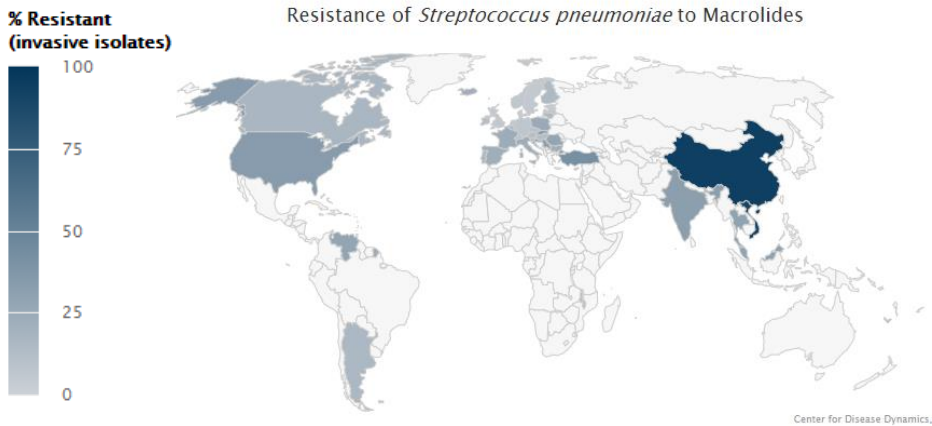
European Comission, AMR Factsheet, 2017

ECDC Data and reports: Antimicrobial resistance and consumption, 2014

K. pneumoniae



S. pneumoniae



Fluoroquinolones

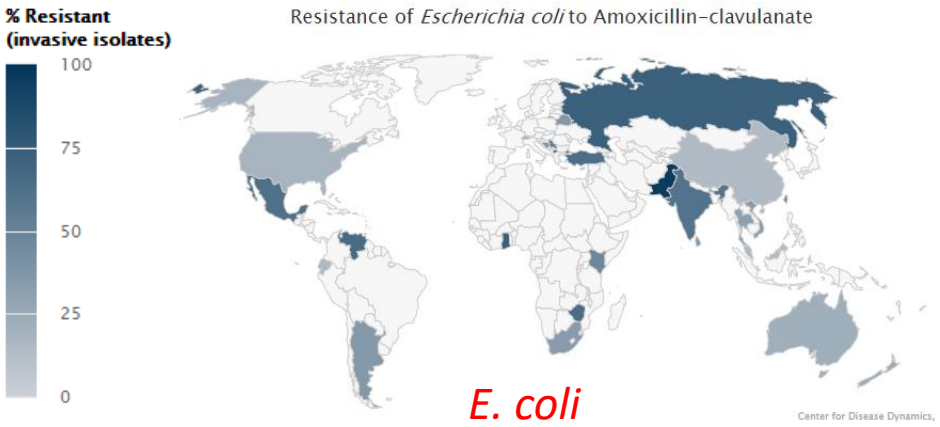
Macrolides

Antibiotic Resistance

Oxacillin (MRSA)

Amoxicillin-clavulanate

S. aureus



E. coli

The Center for Disease, Dynamics Economics & Policy. ResistanceMap: Antibiotic resistance. 2021. https://resistancemap.cddep.org/AntibioticResistance.php. Date accessed: April,15 2021.

AMPs (AntiMicrobial Peptides):

- Short, 7-100 amino acid peptides, active against bacteria, fungi, viruses and even cancer cells
- AMP mode of action: (i) disruption of lipid bilayers; (ii) inhibition of inner-cell processes; (iii) sequestering metal ions (taking part in 'nutritional immunity’)

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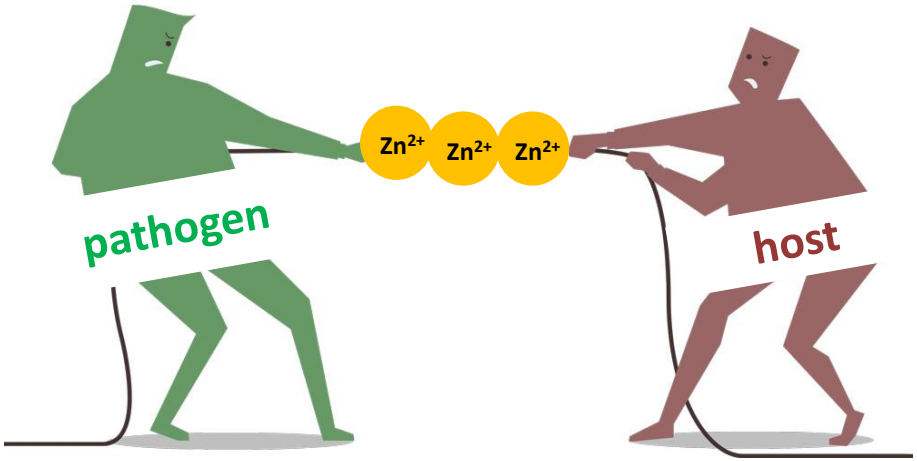
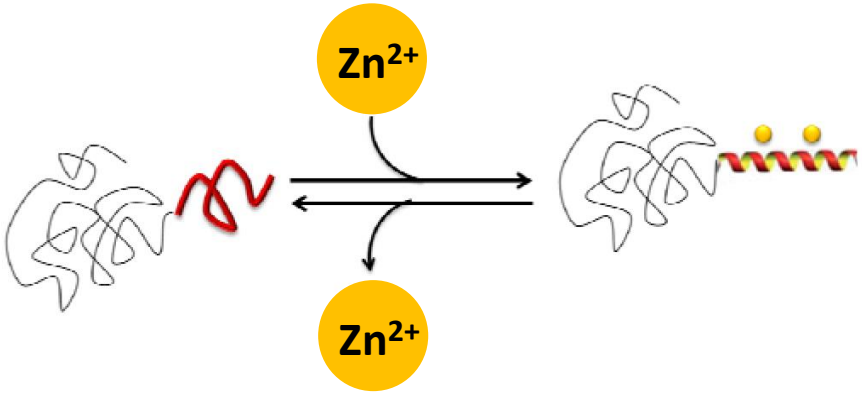
Impact of metal ions on AMP activity:

- AMPs sequester metal ions, so that microbes cannot get enough of them for their survival and virulence



- AMPs need the metal to boost their antimicrobial efficiency, affecting the charge/structure of the peptide



Łoboda D., Kozłowski H., Rowińska-Żyrek M., N J Chem., 2018, 42, 7560

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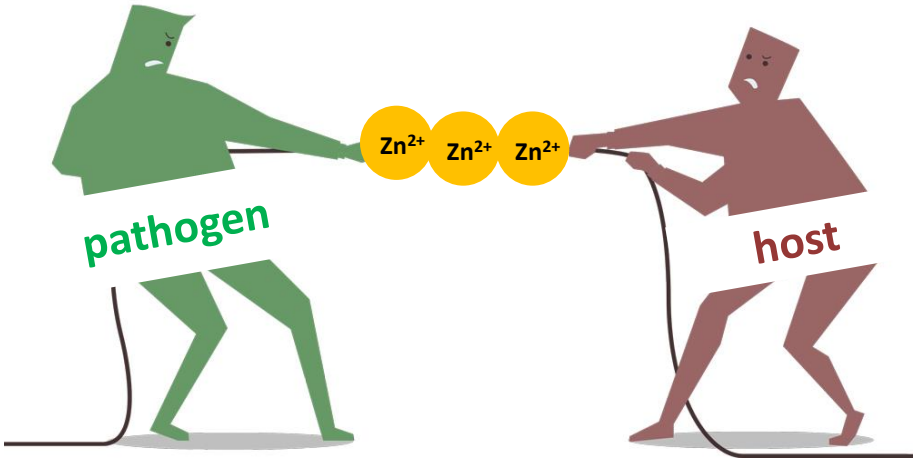

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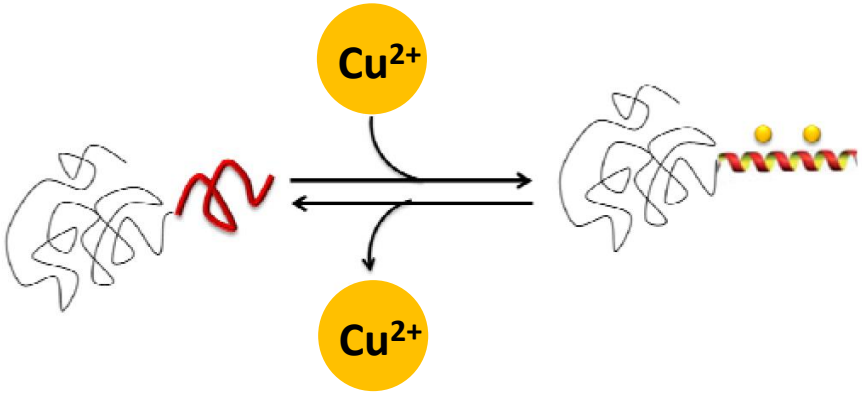

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AMPs enhanced by Zn(II) and Cu(II):

Semenogelins

```
SgI       1  MKPNIIFVLSLLLILEKQAAVMGQKGGSKGRLPSEFSQFPHGQKGQHYSGQKGKQQTESK   60
SgII      1  MKSIILFVLSLLLILEKQAAVMGQKGGSKGQLPSGSSQFPHGQKGQHYFGQKDQQHTKSK   60
SgI      61  GSFSIQYTYHVDANDHDQSRKSQQYDLNALHKTTKSQRHLGGSQQLLHNKQEGRDHDKSK  120
SgII     61  GSFSIQHTYHVDINDHDWTRKSQQYDLNALHKATKSKQHLGGSQQLLNYKQEGRDHDKSK  120
SgI     121  GHFHRVVIHHKGGKAHRGTQNPSQDQGNSPSGKGISSQYSNTEERLWVHGLSKEQTSVSG  180
SgII    121  GHFHMIVIHHKGGQAHHGTQNPSQDQGNSPSGKGLSSQCSNTEKRLWVHGLSKEQASASG  180
SgI     181  AQKGRKQGGSQSSYVLQTEELVANKQQRETKNSHQNKGHYQNVVEVREEHSSKVQTSLCP  240
SgII    181  AQKGRTQGGSQSSYVLQTEELVVNKQQRETKNSHQNKGHYQNVVDVREEHSSKLQTSLHP  240
SgI     241  AHQDKLQHGSKDIFSTQDELLVYNKNQHQTKNLNQDQQHGRKANKISYQSSSTEERRLHY  300
SgII    241  AHQDRLQHGPKDIFTTQDELLVYNKNQHQTKNLSQDQEHGRKAHKISYPSSRTEERQLHH  300
SgI     301  GENGVQKDVSQSSIYS----------------------------------------------  316
SgII    301  GEKSVQKDVSKGSISIQTEEKIHGKSQNQVTIHSQDQEHGHKENKISYQSSSTEERHLNC  360
SgI     316  ----------------------------------------------------------  316
SgII    361  GEKGIQKGVSKGSISIQTEEQIHGKSQNQVRIPSQAQEYGHKENKISYQSSSTEERRLNS  420
SgI     317  ---------------QTEEKAQGKSQKQITIPSQEQEHSQKANKISYQSSSTEERRLHY  360
SgII    421  GEKDVQKGVSKGSISIQTEEKIHGKSQNQVTIPSQDQEHGHKENKMSYQSSSTEERRLNY  480
SgI     361  GENGVQKDVSQRSIYSQTEKLVAGKSQIQAPNPKQEPWHGENAKGESGQSTNREQDLLSH  420
SgII    481  GGKSTQKDVSQSSISFQIEKLVEGKSQIQTPNPNQDQWSGQNAKGKSGQSADSKQDLLSH  540
SgI     421  EQKGRHQHGSHGGLDIVIIEQEDDSDRHLAQHLNNDRNPLFT                    462
SgII    541  EQKGRYKQESSESHNIVITEHEVAQDDHLTQQYNEDRNPIST                    582
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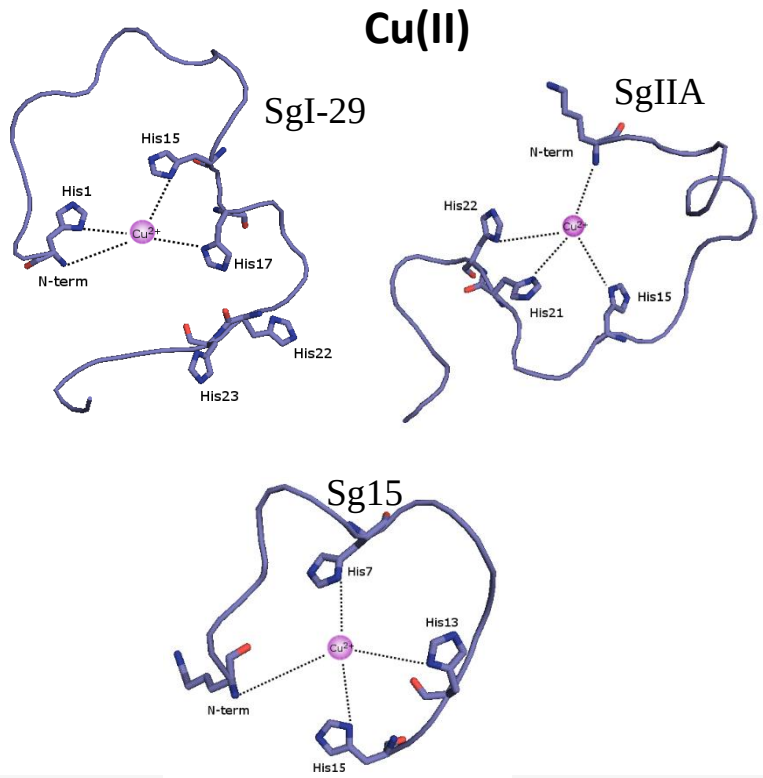

Antimicrobial fragments of semenogelins from the human semen (peptides: SgIIA, SgI-29 and their common 15-aa fragment, Sg-15) bind Zn(II) and Cu(II) ions via a [NH_2, $3N_{im}$] donor set at physiological pH

SgI-29	**HNKQEGRDHDKSKGHFHRVVIHHKGGKAH**
SgIIA	**KQEGRDHDKSKGHFHMIVIHHKGGQAHHG**
Sg-15	**KQEGRDHDKSKGHFH**

Dorota Dudek, Adriana Miller, Aleksandra Hecel, Arian Kola, Daniela Valensin, Aleksandra Mikołajczyk, Miquel Barcelo-Oliver, Agnieszka Matera-Witkiewicz, Magdalena Rowińska-Żyrek, Inorganic Chemistry, 2023, https://pubs.acs.org/doi/10.1021/acs.inorgchem.3c02390

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SgII     61  GSFSIQHTYHVDINDHDWTRKSQQYDLNALHKATKSKQHLGGSQQLLNYKQEGRDHDKSK  120
SgI     121  GHFHRVVIHHKGGKAHRGTQNPSQDQGNSPSGKGISSQYSNTEERLWVHGLSKEQTSVSG  180
SgII    121  GHFHMIVIHHKGGQAHHGTQNPSQDQGNSPSGKGLSSQCSNTEKRLWVHGLSKEQASASG  180
SgI     181  AQKGRKQGGSQSSYVLQTEELVANKQQRETKNSHQNKGHYQNVVEVREEHSSKVQTSLCP  240
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SgI     241  AHQDKLQHGSKDIFSTQDELLVYNKNQHQTKNLNQDQQHGRKANKISYQSSSTEERRLHY  300
SgII    241  AHQDRLQHGPKDIFTTQDELLVYNKNQHQTKNLSQDQEHGRKAHKISYPSSRTEERQLHH  300
SgI     301  GENGVQKDVSQSSIYS----------------------------------------------  316
SgII    301  GEKSVQKDVSKGSISIQTEEKIHGKSQNQVTIHSQDQEHGHKENKISYQSSSTEERHLNC  360
SgI     316  ----------------------------------------------------------  316
SgII    361  GEKGIQKGVSKGSISIQTEEQIHGKSQNQVRIPSQAQEYGHKENKISYQSSSTEERRLNS  420
SgI     317  ---------------QTEEKAQGKSQKQITIPSQEQEHSQKANKISYQSSSTEERRLHY  360
SgII    421  GEKDVQKGVSKGSISIQTEEKIHGKSQNQVTIPSQDQEHGHKENKMSYQSSSTEERRLNY  480
SgI     361  GENGVQKDVSQRSIYSQTEKLVAGKSQIQAPNPKQEPWHGENAKGESGQSTNREQDLLSH  420
SgII    481  GGKSTQKDVSQSSISFQIEKLVEGKSQIQTPNPNQDQWSGQNAKGKSGQSADSKQDLLSH  540
SgI     421  EQKGRHQHGSHGGLDIVIIEQEDDSDRHLAQHLNNDRNPLFT                    462
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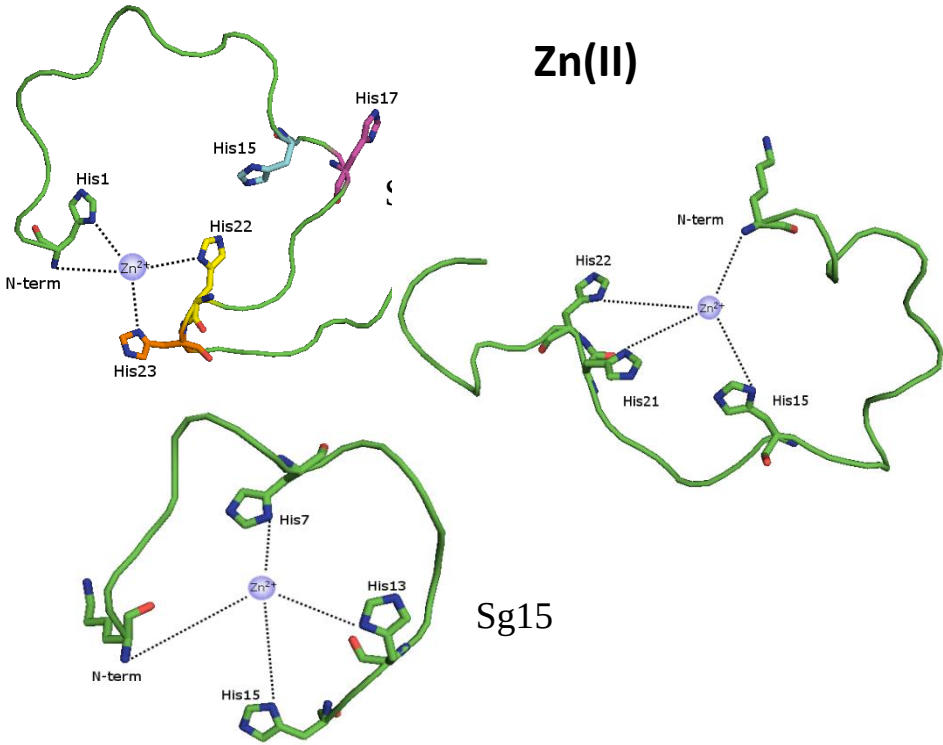

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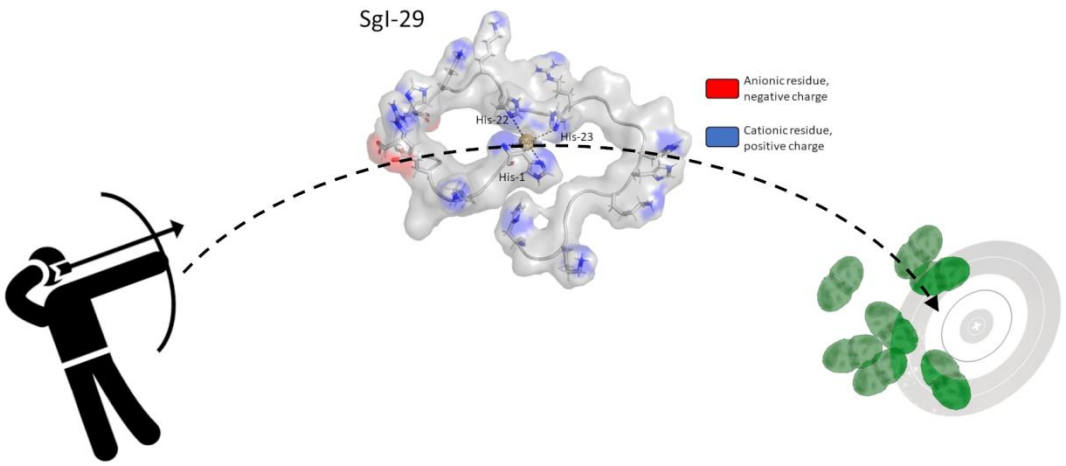

	Enterococcus faecalis
	MIC (μg/mL)
Sg-15	n/s
Sg-15-Cu(II)	256
Sg-15-Zn(II)	n/s
SgI-29	256
SgI-29-Cu(II)	256
SgI-29-Zn(II)	256
SgIIA	n/s
SgIIA-Cu(II)	256
SgIIA-Zn(II)	256

Zn(II) and Cu(II) binding enhances semenogelins' antimicrobial activity., most probably due to **increase of the cathionic character of the complexes**, that enable their interaction with negatively charged bacterial membranes.

In the case of the two native semenogelin fragment metal complexes, **the strong local positive charge in the metal-bound HH motif correlates well with their antimicrobial activity.**

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PvHCt – an antimicrobial shrimp peptide

Peptide sequence:

FEDLPNFGHIQVKVFNHGEHIHH

Mass spectrometry:

Stoichiometry of the Zn(II) and Cu(II)-PvHCt complexes is 1:1

Whiteleg shrimp
(*Litopenaeus vannamei*)

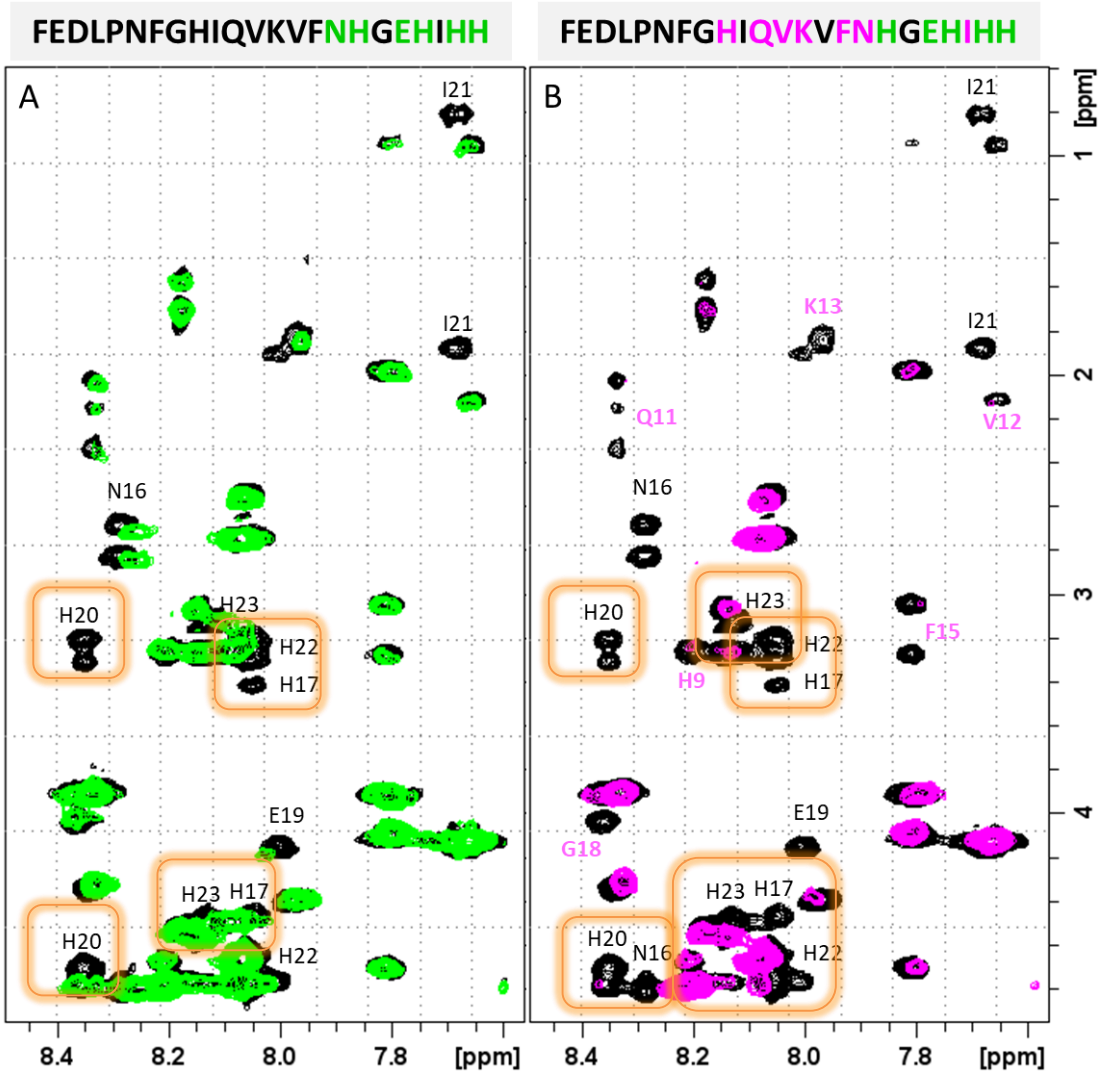
Potentiometric and spectroscopic studies:

Suggested modes of coordination (pH 7.4)

Zn(II) complexes: 3 N_{im} /4 N_{im}

Cu(II) complexes: 2 N^-, 1 N_{im}

PvHCt: metal binding sites are indicated by NMR

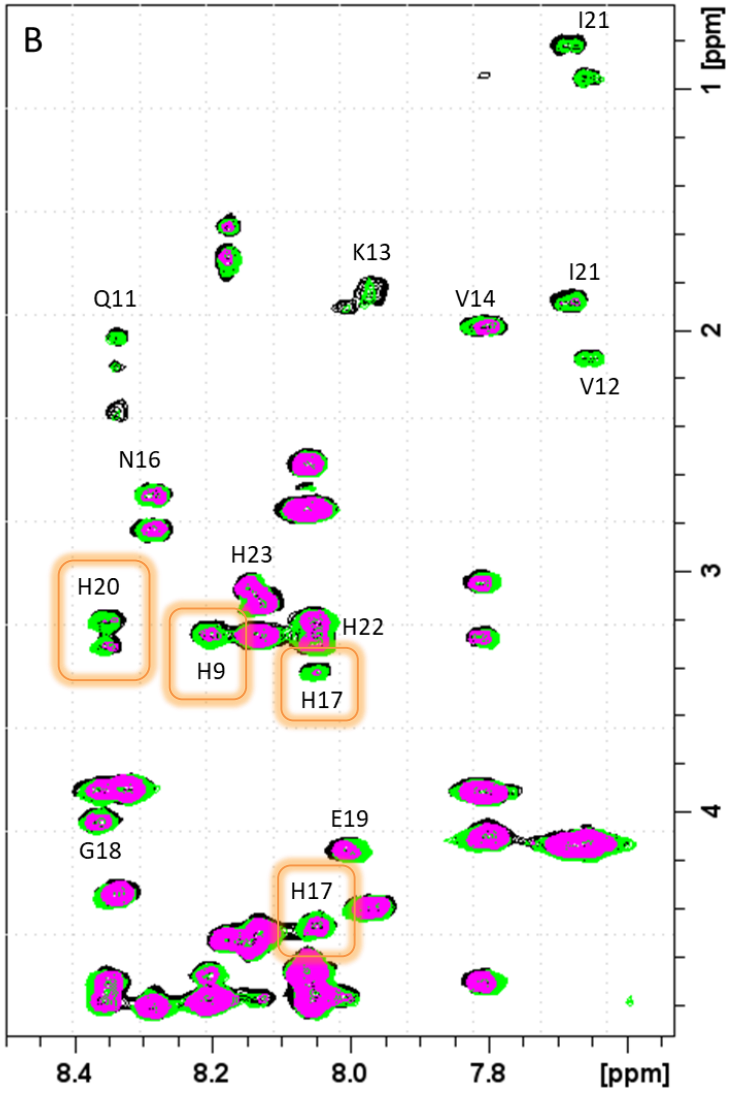


Zn(II) complexes:

- no metal addition
- 0.2 eq Zn(II)
- 0.6 eq Zn(II)

Changes for H17, H20, H22, H23 residues

PvHCt: metal binding sites are indicated by NMR



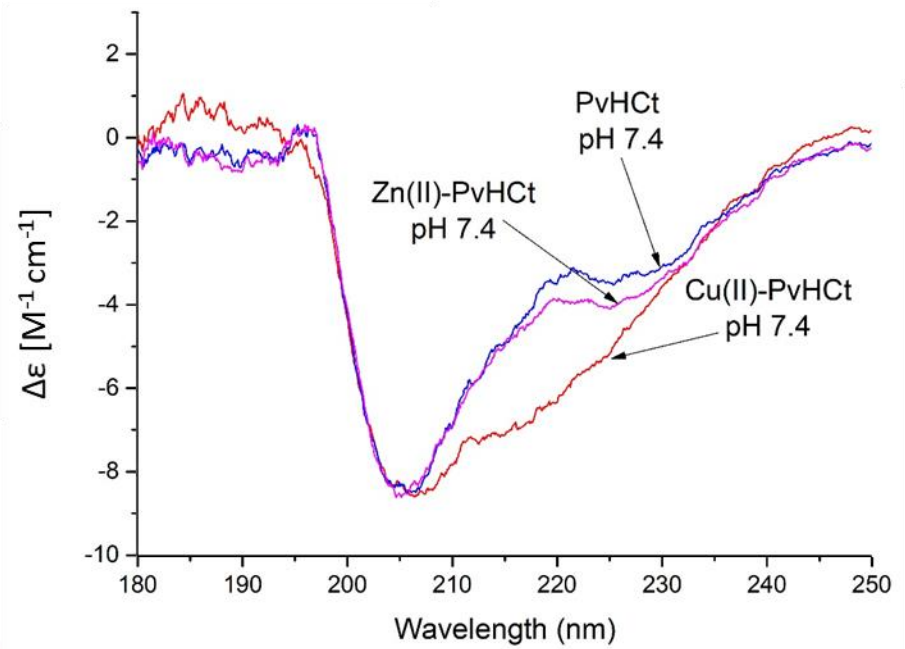
Cu(II) complexes:

- no metal addition
- 0.1 eq Cu(II)
- 0.2 eq Cu(II)

Changes for H9, H17, H20 residues

FEDLPNFGHIQVKVFNHGEHIHH

PvHCt: Cu(II) induces a structural change



Whiteleg shrimp
(*Litopenaeus vannamei*)

PvHCt: Cu(II) triggers antimicrobial activity

	Escherichia coli **ATCC 25922**	**MRSA ATCC 43300**	***Enterococcus faecalis*** **ATCC 29212**
	MIC_{50} [µg/mL]	MIC_{50} [µg/mL]	MIC_{50} [µg/mL]
PvHCt	n/s	n/s	n/s
Zn(II)-PvHCt	n/s	32	512
Cu(II)-PvHCt	16	16	16

Whiteleg shrimp
(*Litopenaeus vannamei*)

PvHCt: Cu(II) triggers antimicrobial activity

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Cu(II)-PvHCt	16	16	16

Whiteleg shrimp
(*Litopenaeus vannamei*)

- PvHCt shows antimicrobial activity only in presence of metal ions
- Cu(II) drasticly increases the biological activity of PvHCt peptide

Clavanins

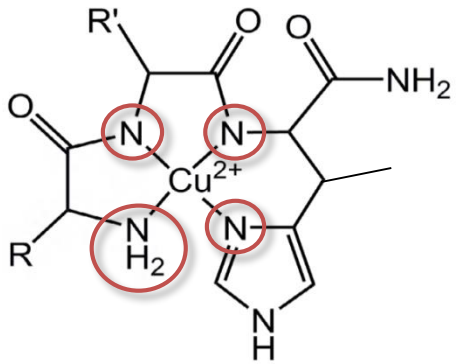
Clavanin A:
VFQFLGKIIHHVGNFVHGFSHVF-COOH

Clavanin B:
VFQFLGRIIHHVGNFVHGFSHVF-COOH

Clavanin C:
VFHLLGKIIHHVGNFVYGFSHVF-COOH

Clavanin D:
AFKLLGRIIHHVGNFVYGFSHVF-COOH

Clavanin E:
LFKLLGKIIHHVGNFVHGFSHVF-COOH



Mass spectrometry:

Stoichiometry of the Zn(II) and Cu(II)-clavanin complexes is 1:1

Potentiometric titrations, NMR, UV-Vis and CD spectroscopy :

Suggested coordination modes

Zn(II) complexes (physiological pH): 3 N_{im}

Cu(II) complexes (physiological pH): 3 N_{im}, 1 N^-

Cu(II) complexes (higher pH): 1 N_{im}, 3 N^-

Cu(II) complexes of ClavC: NH_2, 2 N^-, 1 N_{im}

Miller Adriana, Mikołajczyk Aleksandra, Matera-Witkiewicz Agnieszka, Wieczorek Robert, Rowińska-Żyrek Magdalena The chemical 'butterfly effect' explains the coordination chemistry and antimicrobial properties of clavanin complexes, Inorganic Chemistry, 2021, 60, 12730-12734

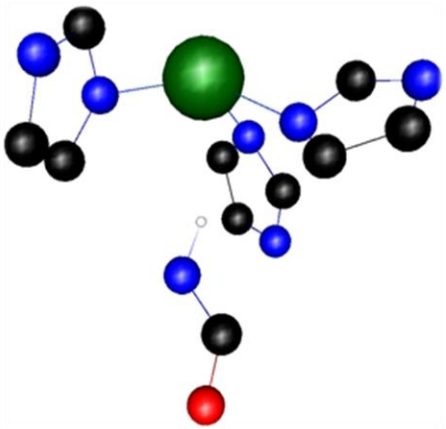
Clavanins: antimicrobial efficiency at physiological pH

Strain	*Escherichia coli (-) ATCC 25922*	*Enterococcus faecalis (+) ATCC 29212*	*Staphylococcus aureus (+) ATCC 43300*	*Candida albicans* ATCC 10231
	MIC (µg/mL)	MIC (µg/mL)	MIC (µg/mL)	MIC (µg/mL)
Clavanin A	n/d	256	n/d	128
Cu(II)-Clavanin A	n/d	n/d	n/d	128
Zn(II)-Clavanin A	256	256	n/d	64
Clavanin B	256	256	n/d	64
Cu(II)-Clavanin B	256	**8**	n/d	64
Zn(II)-Clavanin B	n/d	**8**	n/d	128
Clavanin C	n/d	128	128	64
Cu(II)-Clavanin C	128	256	128	64
Zn(II)-Clavanin C	**16**	**64**	**16**	**16**
Clavanin D	**64**	128	128	**16**
Cu(II)-Clavanin D	256	128	128	32
Zn(II)-Clavanin D	256	128	128	64
Clavanin E	n/d	n/d	n/d	32
Cu(II)-Clavanin E	256	n/d	n/d	32
Zn(II)-Clavanin E	n/d	n/d	**64**	**16**

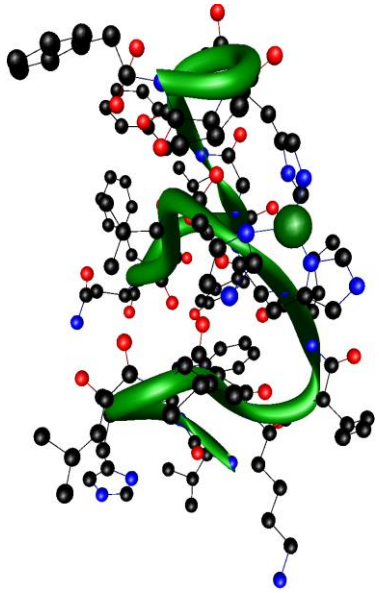
Zn(II)-Clavanin C: The highest activity of the whole clavanin family is observed, no metal-enhanced trend

Clavanins: DFT calculations, Zn(II), pH 7.4

● C ● O ● N ○ H ● Zn



Zn(II)-clavanin C
(structure of the binding site)



Zn(II)-clavanin C

Clavanin A:
VFQFLGKIIHHVGNFVHGFSHVF-COOH

Clavanin B:
VFQFLGRIIHHVGNFVHGFSHVF-COOH

Clavanin C:
VFHLLGKIIHHVGNFVYGFSHVF-COOH

Clavanin D:
AFKLLGRIIHHVGNFVYGFSHVF-COOH

Clavanin E:
LFKLLGKIIHHVGNFVHGFSHVF-COOH

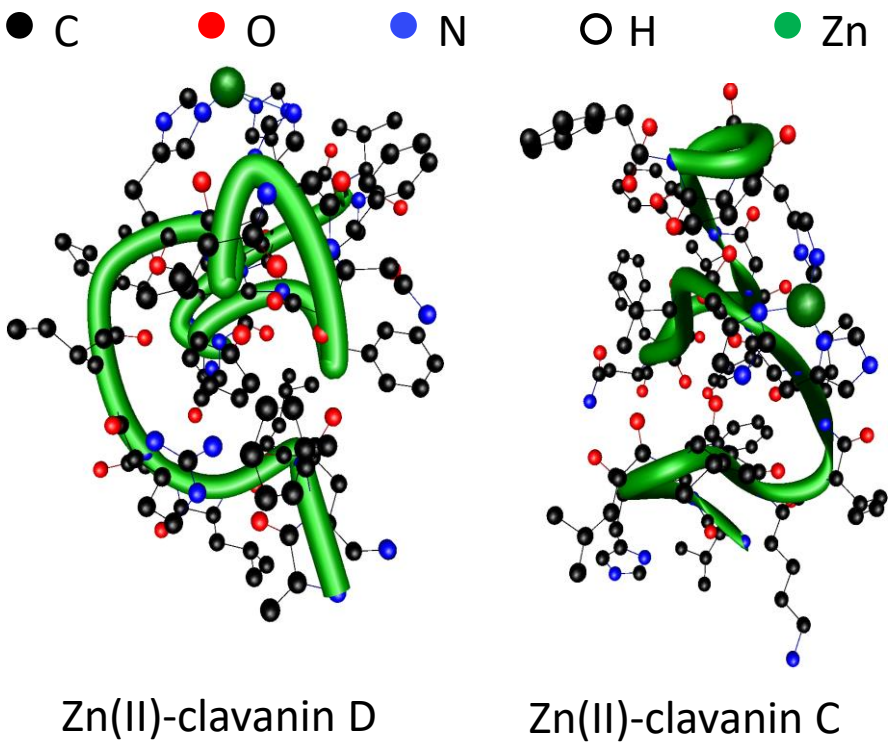
Zn(II)-clavanin A, B, E: His10, His11 and His17 imidazoles

Zn(II)-clavanin C, D: His10, His11 and His21 imidazoles

The O=C-N-H fragment is directly below the Zn(II) ion and aims its hydrogen atom at the positively charged metal cation, pushing it out of its binding pocket = **the longest** (and most labile) **metal-ligand bonds** = easy metal dissociation

Miller Adriana, Mikołajczyk Aleksandra, Matera-Witkiewicz Agnieszka, Wieczorek Robert, Rowińska-Żyrek Magdalena The chemical 'butterfly effect' explains the coordination chemistry and antimicrobial properties of clavanin complexes, Inorganic Chemistry, 2021, 60, 12730-12734

Clavanins: DFT calculations, Zn(II), pH 7.4



Zn(II)-clavanin D Zn(II)-clavanin C

Clavanin A:
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Clavanin E:
LFKLLGKIIHHVGNFVHGFSHVF-COOH

Zn(II)-clavanin A, B, E: His10, His11 and His17 imidazoles

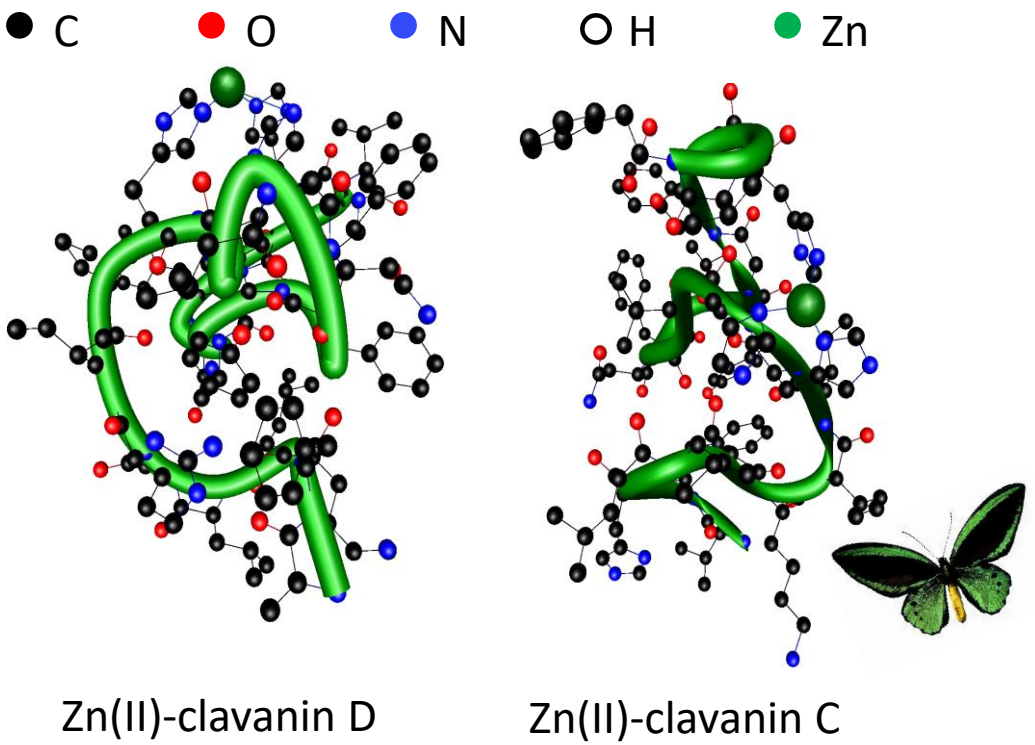
Zn(II)-clavanin C, D: His10, His11 and His21 imidazoles

Pushing the metal out of its binding pocket was observed only for Zn(II)-ClavC. The different organization of the binding pocket is most likely due to the **pre-folding of the clavanin C peptide** before the addition of Zn(II) ions.

	ClavA	ClavB	ClavC	ClavD	ClavE
His10	2.106	2.107	2.170	2.164	2.192
His11	2.017	2.008	2.196	2.193	2.070
His17	2.038	2.016			2.054
His21			2.199	2.030	

Metal – ligand distances (in angstroms) for clavanin A, B, C, D, E and Zn(II) complexes

Clavanins: DFT calculations, Zn(II), pH 7.4



Zn(II)-clavanin D Zn(II)-clavanin C

Clavanin A:
VFQFLGKIIHHVGNFVHGFSHVF-COOH

Clavanin B:
VFQFLGRIIHHVGNFVHGFSHVF-COOH

Clavanin C:
VFHLLGKIIHHVGNFVYGFSHVF-COOH

Clavanin D:
AFKLLGRIIHHVGNFVYGFSHVF-COOH

Clavanin E:
LFKLLGKIIHHVGNFVHGFSHVF-COOH

Zn(II)-clavanin A, B, E: His10, His11 and His17 imidazoles

Zn(II)-clavanin C, D: His10, His11 and His21 imidazoles

Pushing the metal out of its binding pocket was observed only for Zn(II)-ClavC. The different organization of the binding pocket is most likely due to the **pre-folding of the clavanin C peptide** before the addition of Zn(II) ions.

	ClavA	ClavB	ClavC	ClavD	ClavE
His10	2.106	2.107	2.170	2.164	2.192
His11	2.017	2.008	2.196	2.193	2.070
His17	2.038	2.016			2.054
His21			2.199	2.030	

Metal – ligand distances (in angstroms) for clavanin A, B, C, D, E and Zn(II) complexes

Amylin and pramlintide

- Amylin (IAPP, *Islet Amyloid Polypeptide)* co-secreted with insulin from beta Langerhans cells of the pancreas
- Amyloid islets are present in 95% of type II diabetes patients
- In pramlintide, a non-fibrillating amylin analouge used in a T2D treatment, in which, as in the case of rat amylin, Ala25, Ser28 and Ser29 were substituted by proline residues, what resulted in the reduction of fibrilization

Biol. Chem., Vol. 393, pp. 641–646, July 2012 • Copyright © by Walter de Gruyter • Berlin • Boston. DOI 10.1515/hsz-2012-0107

Short Communication

Antimicrobial activity of human islet amyloid polypeptides: an insight into amyloid peptides' connection with antimicrobial peptides

Effective against:
- *E. coli*
- *S. aureus*

Human amylin:	KCNTATCATQRLANFLVHSSNNFGAILSSTNVGSNTY-NH_2
Rat amylin:	KCNTATCATQRLANFLVRSSNNLGPVLPPTNVGSNTY-NH_2
Pramlintide:	KCNTATCATQRLANFLVHSSNNFGPILPPTNVGSNTY-NH_2

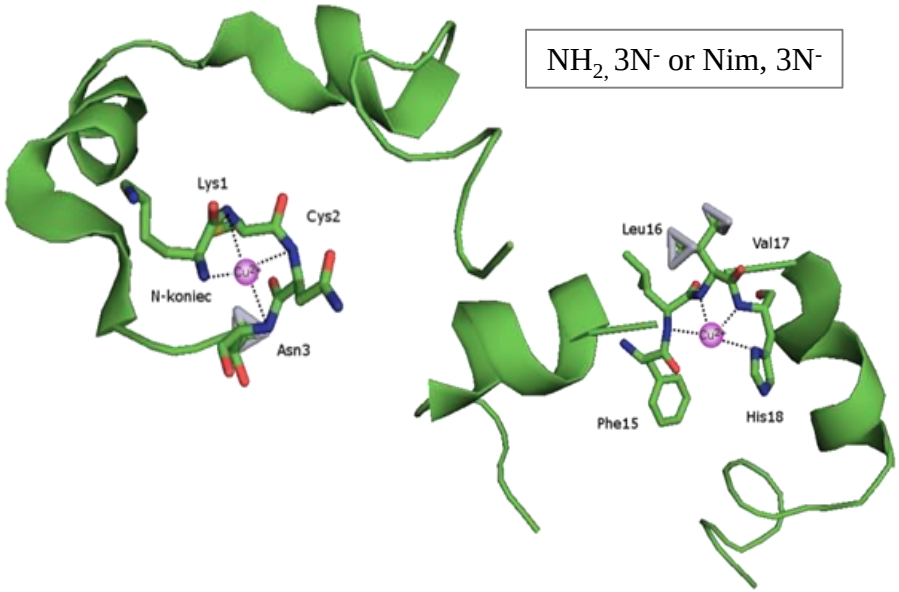
Pramlintide

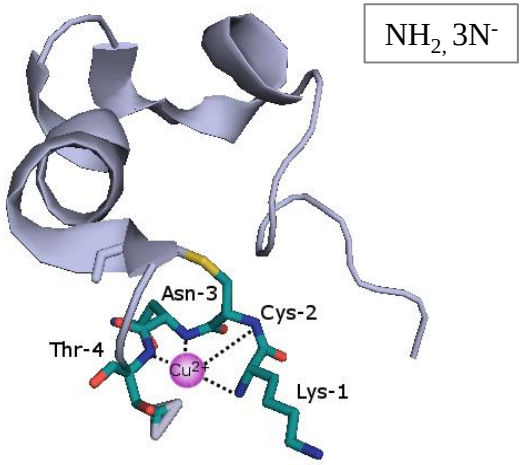
KCNTATCATQRLANFLVHSSNNFGPILPPTNVGSNTY-NH_2

Rat amylin

KCNTATCATQRLANFLVRSSNNLGPVLPPTNVGSNTY-NH_2

Cu(II)





Dudek Dorota, Alghrably Mawadda, Emwas Abdul-Hamid, Jaremko Łukasz, Jaremko Mariusz, Rowińska-Żyrek Magdalena, Copper(II) and amylin analogues: a complicated relationship, Inorganic Chemistry, 2020, 59, 2527-2535

Pramlintide

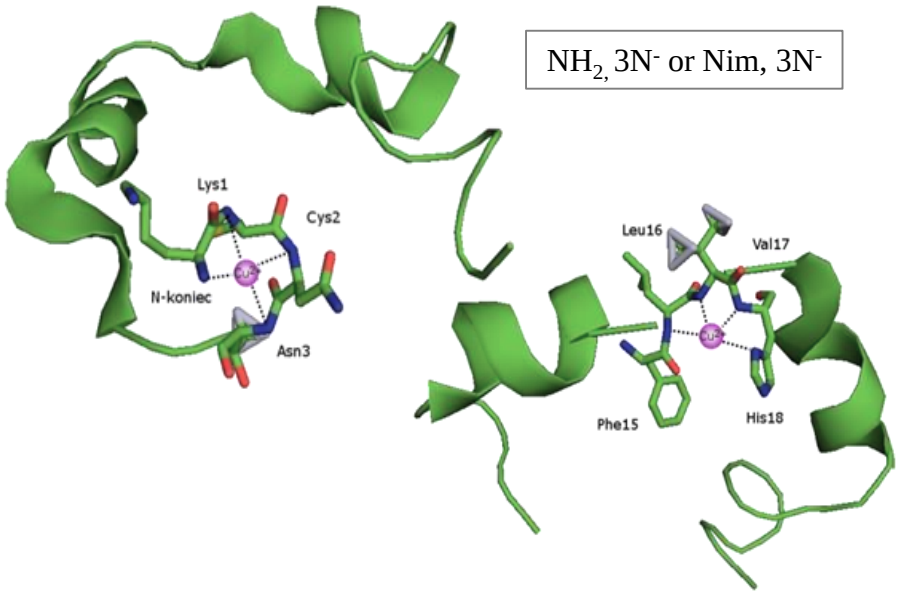
KCNTATCATQRLANFLVHSSNNFGPILPPTNVGSNTY-NH_2

Rat amylin

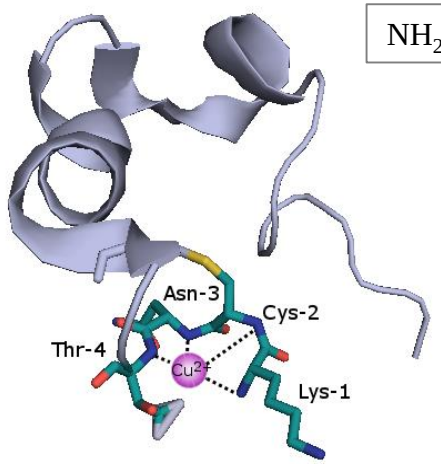
KCNTATCATQRLANFLVRSSNNLGPVLPPTNVGSNTY-NH_2

Cu(II)

NH_2, $3N^-$ or Nim, $3N^-$

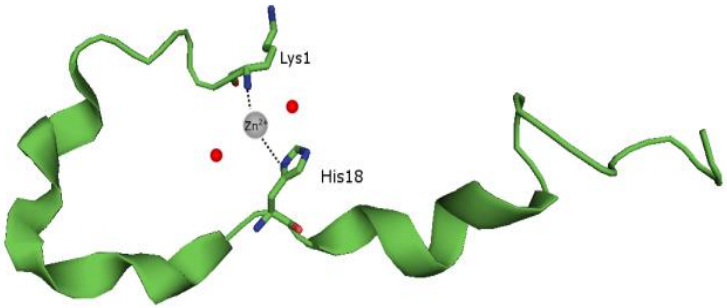


NH_2, $3N^-$

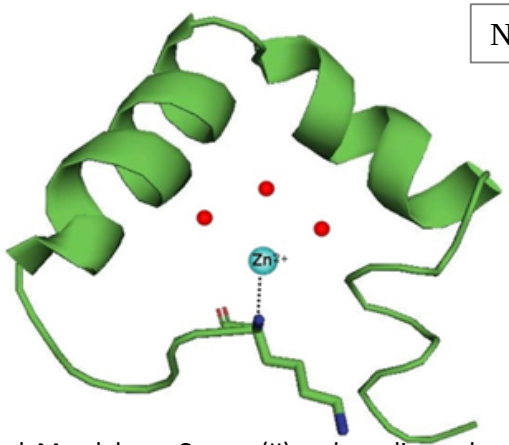


Zn(II)

NH_2, Nim



NH_2



Dudek Dorota, Alghrably Mawadda, Emwas Abdul-Hamid, Jaremko Łukasz, Jaremko Mariusz, Rowińska-Żyrek Magdalena, Copper(II) and amylin analogues: a complicated relationship, Inorganic Chemistry, 2020, 59, 2527-2535

Dudek Dorota, Dzień Emilia, Mikołajczyk Aleksandra, Matera-Witkiewicz Agnieszka, Hajda Agata, Olesiak-Bańska Joanna, Rowińska-Żyrek Magdalena, Zn(II) binding to pramlintide results in a structural kink, fibril formation and antifungal activity, Scientific Reports, 2022, 12, 20543/1-20543/8

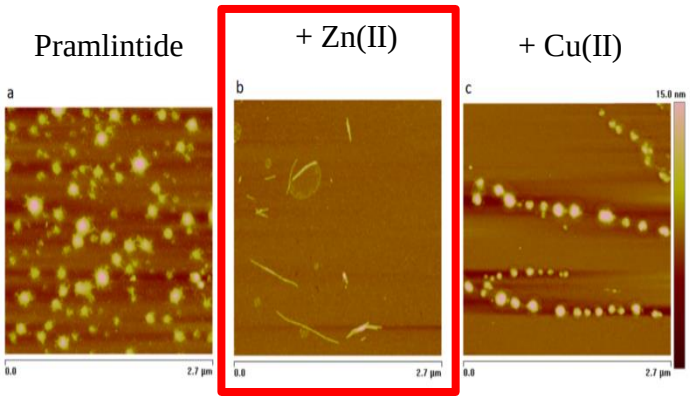
Antimicrobial activity

Strain	*Escherichia coli* ATCC 25922	*Staphylococcus aureus ATCC 43300*	*Candida albicans* ATCC 10231
	MIC (ug/mL)	MIC (ug/mL)	MIC (ug/mL)
rat amylin	n/d	n/d	n/d
Cu(II)-rat amylin	n/d	n/d	n/d
Zn(II)-rat amylin	n/d	n/d	n/d
pramlintide	n/d	n/d	n/d
Cu(II)-pramlintide	n/d	n/d	n/d
Zn(II)-pramlintide	n/d	n/d	**256**
Ac-pramlintide	n/d	n/d	n/d
Cu(II)-Ac-pramlintide	n/d	n/d	n/d
Zn(II)-Ac-pramlintide	n/d	n/d	n/d

Dudek Dorota, Dzień Emilia, Mikołajczyk Aleksandra, Matera-Witkiewicz Agnieszka, Hajda Agata, Olesiak-Bańska Joanna, Rowińska-Żyrek Magdalena, Zn(II) binding to pramlintide results in a structural kink, fibril formation and antifungal activity, Scientific Reports, 2022, 12, 20543/1-20543/8

Pramlintide forms amyloid fibrils in the presence of Zn(II)

24h



Human amylin:	KCNTATCATQRLANFLVHSSNNFGAILSSTNVGSNTY-NH_2
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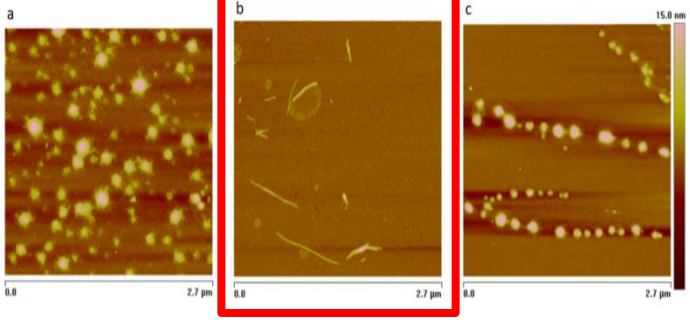
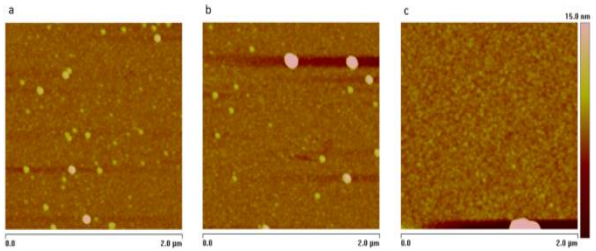
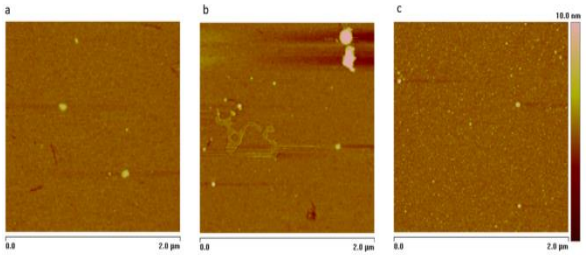
Pramlintide + Zn(II) + Cu(II)



Ac -Pramlintide + Zn(II) + Cu(II)



Rat amylin + Zn(II) + Cu(II)



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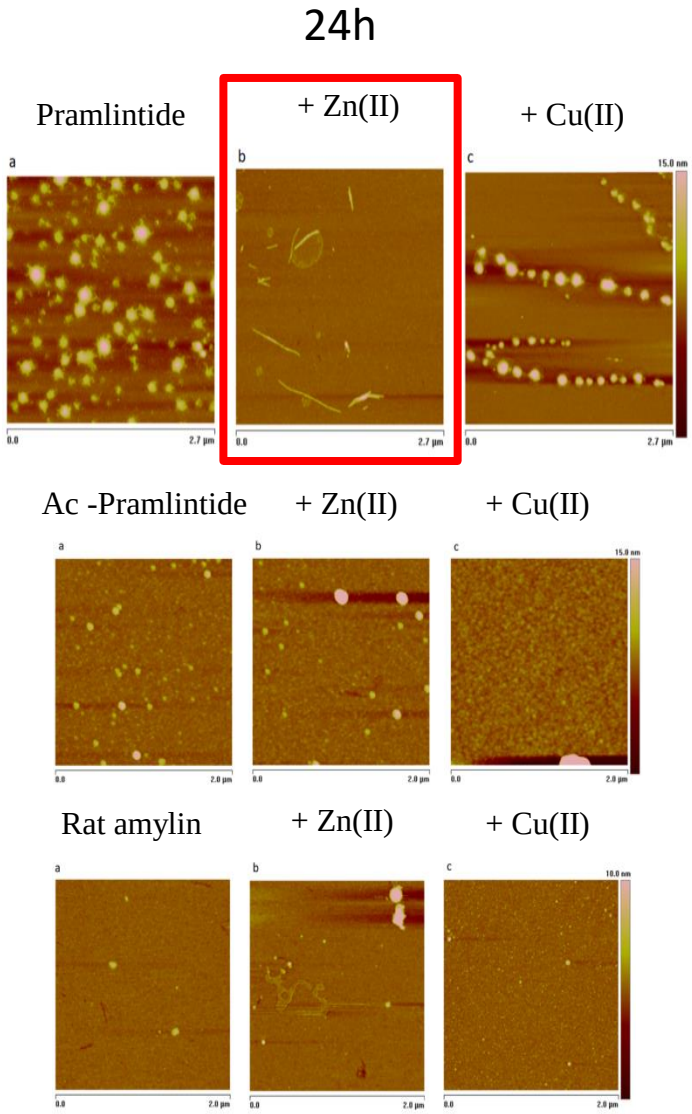
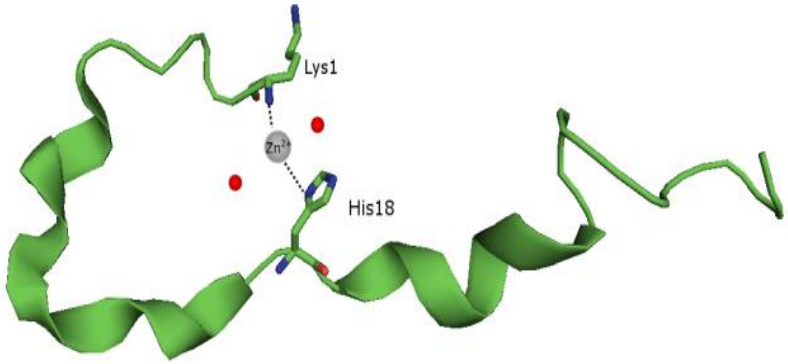
Conclusions: pramlintide





Zn(II) cooordination to pramlintide induces a kink in the pramlintide structure, triggering fibril formation and most likely making the complex act like a needle that could disrupt *C. albicans* cell wall

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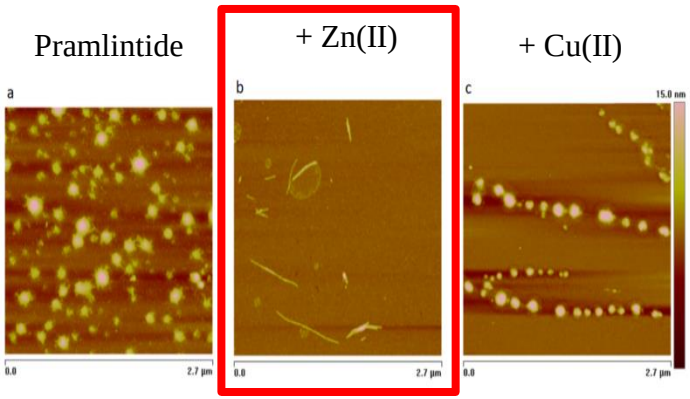

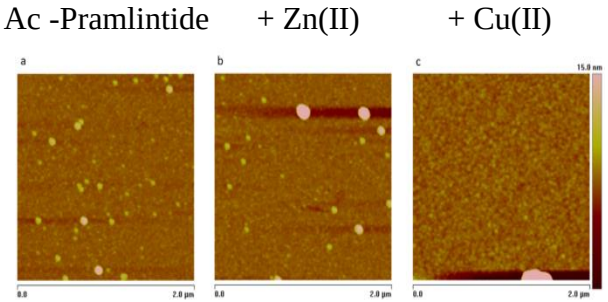

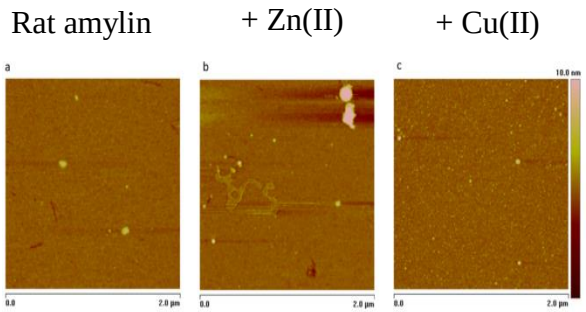

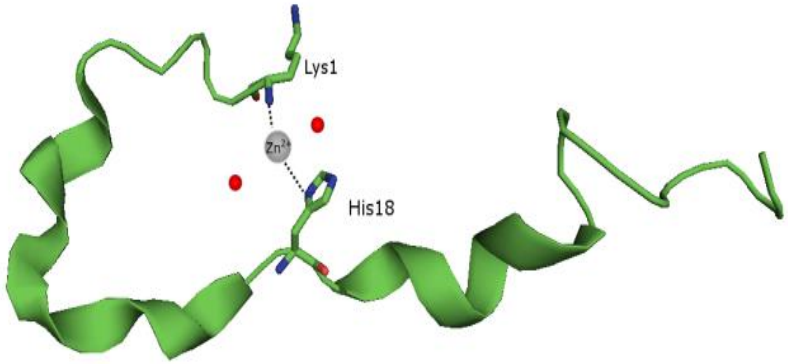

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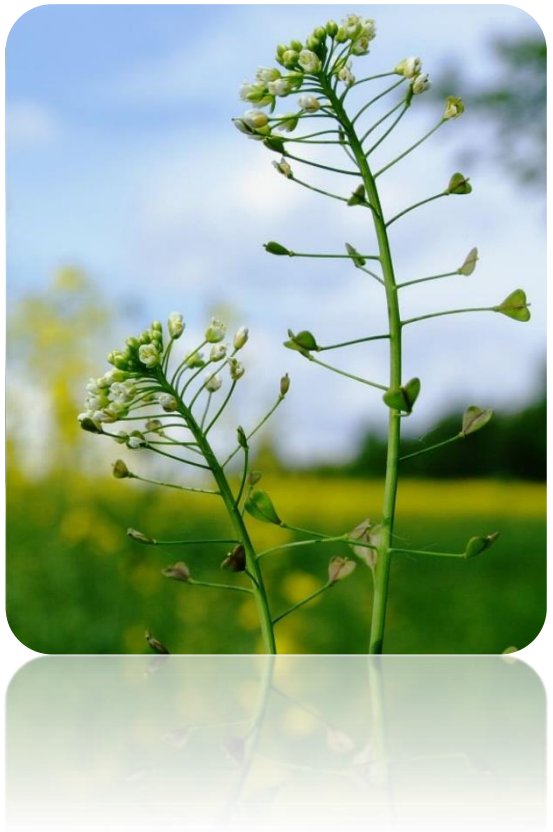
Shepherin forms amyloid fibrils in the presence of Zn(II)

Shepherin: GYGGHGGHGGHGGHGGHGGHGHGGGGHG



Wątły Joanna, Szarszoń Klaudia, Mikołajczyk Aleksandra, Grelich-Mucha Manuela, Matera-Witkiewicz Agnieszka, Olesiak-Bańska Joanna, Rowińska-Żyrek Magdalena, Inorganic Chemistry, 2023, 62, 19786-19794

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Antimicrobial activity (MIC [µg/mL])

	C. albicans ATCC 10231	E. coli ATCC 25922	MRSA ATCC 43300	P. aeruginosa ATCC 27853	E. faecalis ATCC 29212	K. pneumoniae ATCC 700603	A. baumannii ATCC 19606
Shep I	n/d	n/d	n/d	n/d	n/d	n/d	n/d
Shep I – Cu(II)	n/d	n/d	n/d	n/d	n/d	n/d	n/d
Shep I – Zn(II)	*16*	n/d	n/d	n/d	n/d	n/d	n/d

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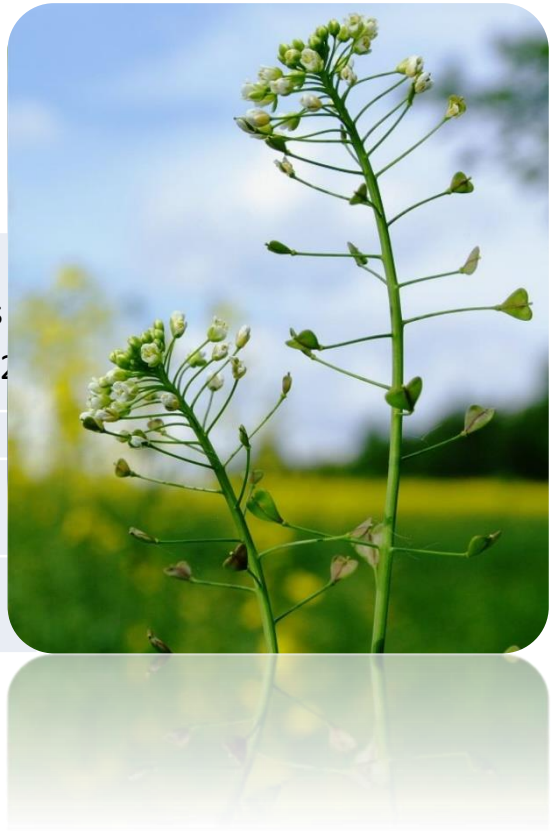

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Shep I – Cu(II)	n/d	n/d	n/d	n/d	n/d
Shep I – Zn(II)	*16*	n/d	n/d	n/d	n/d

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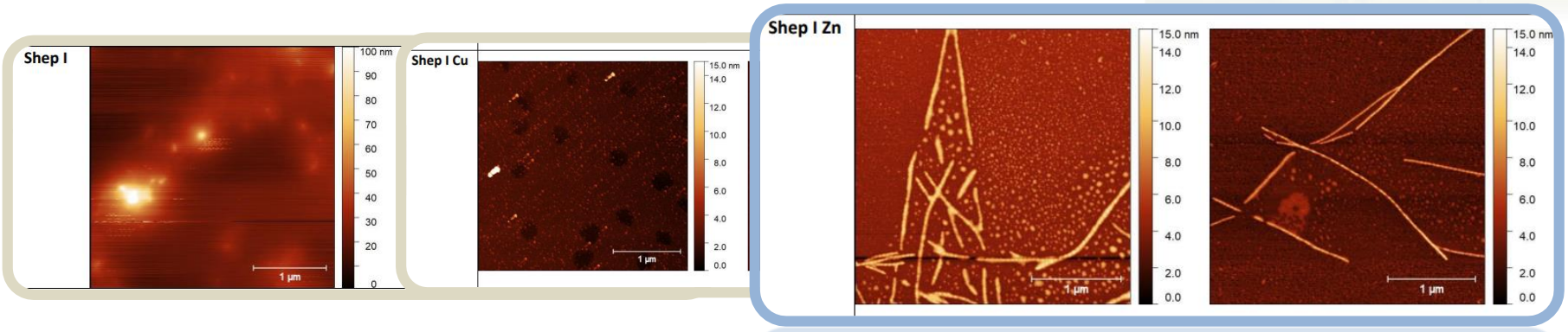
Ligand pH 7 → addition of Zn(II) → beta sheet structure → **fibrils only in case of Zn(II)-shepherin complex**



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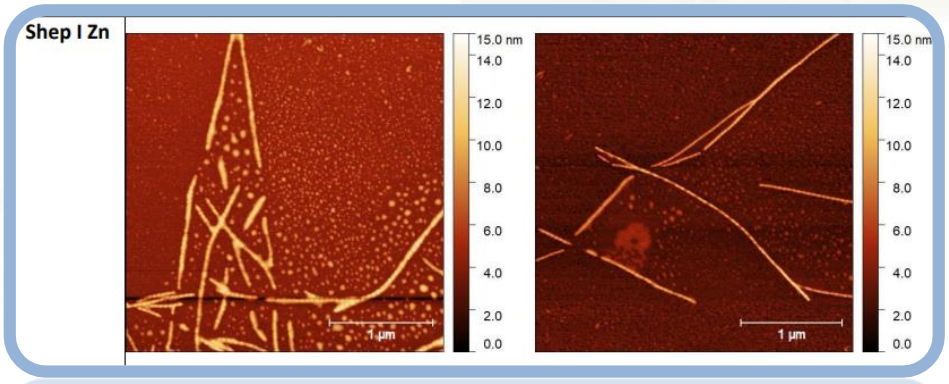

How to use this knowledge?

- In a rational design of novel AMP-metal complexes with **enhanced features which contibute to their antimicrobial efficiency**

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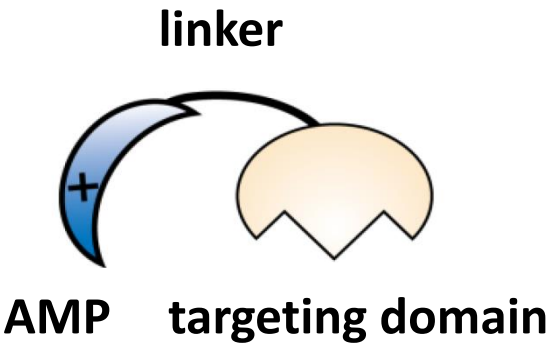
- By attaching AMP complexes to commercially used drugs or appropriately designed **targeting domains**



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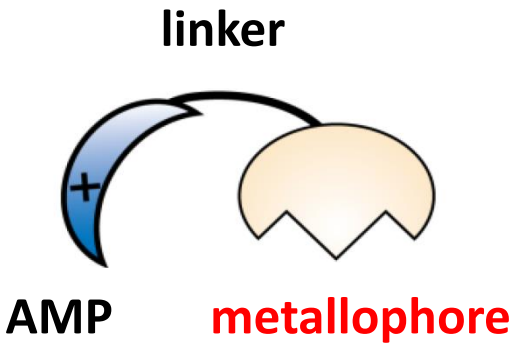
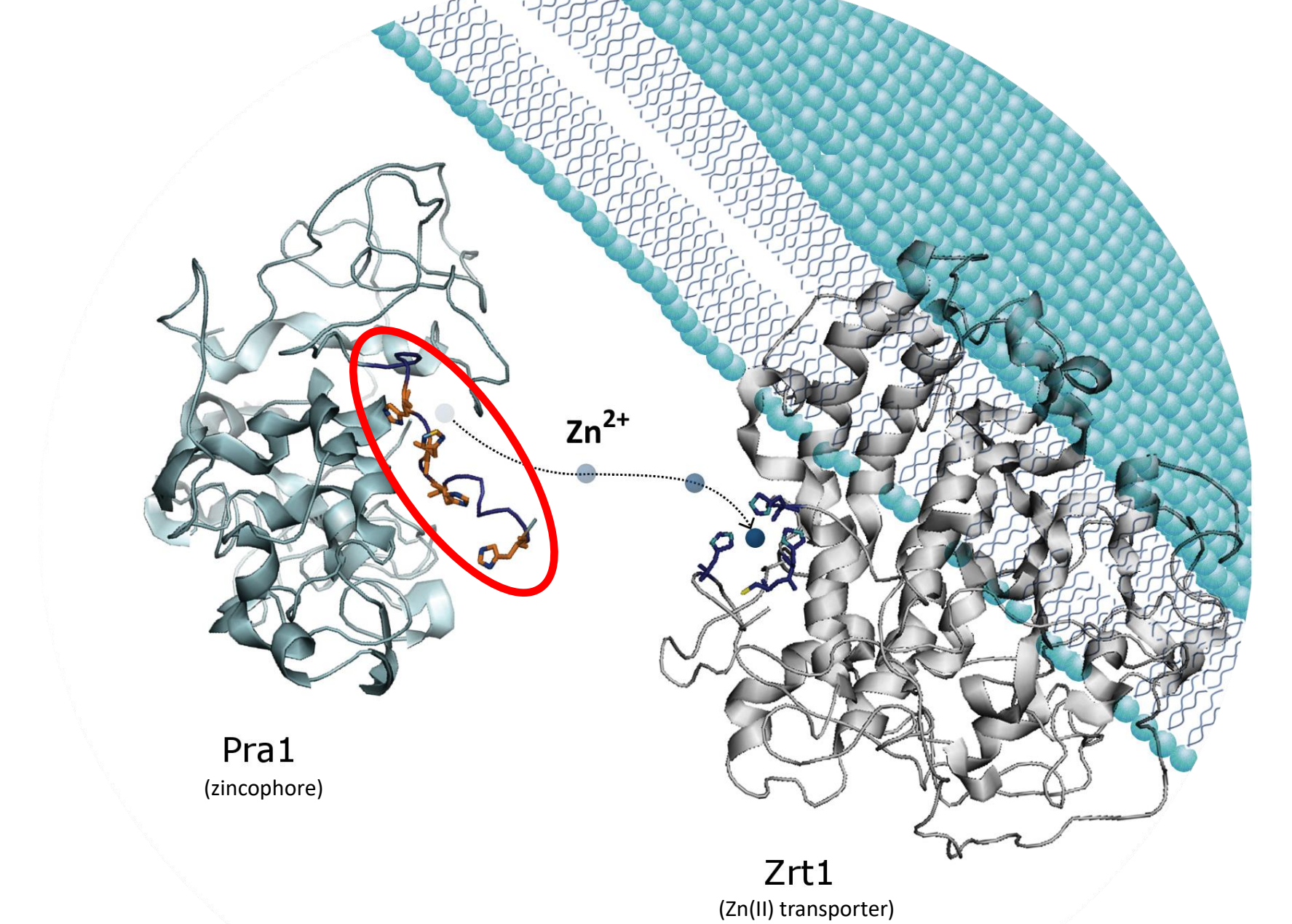
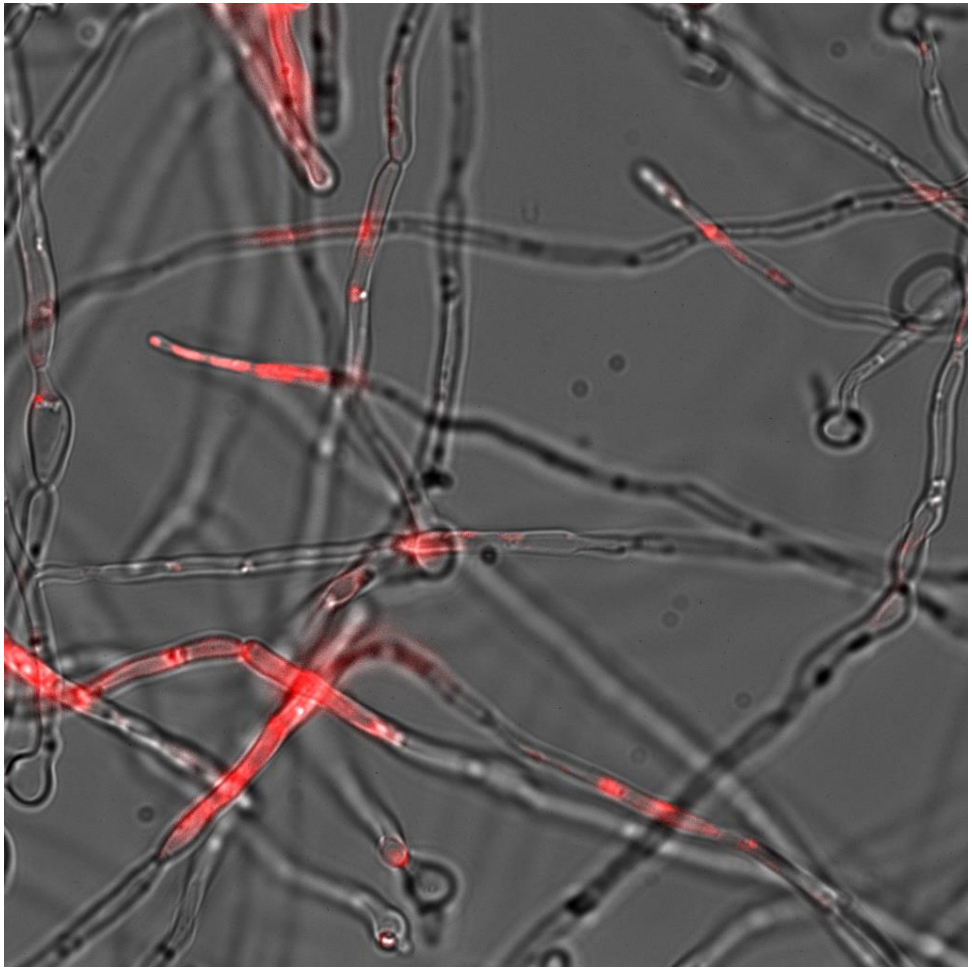




Garstka K., Potoczniak G., Kozłowski H., Rowińska-Żyrek M., Dalton Transactions, 2024, 53, 2848-2858

Łoboda D., Rowińska-Żyrek M., Dalton Transactions, 2018, 47, 2646-2654.

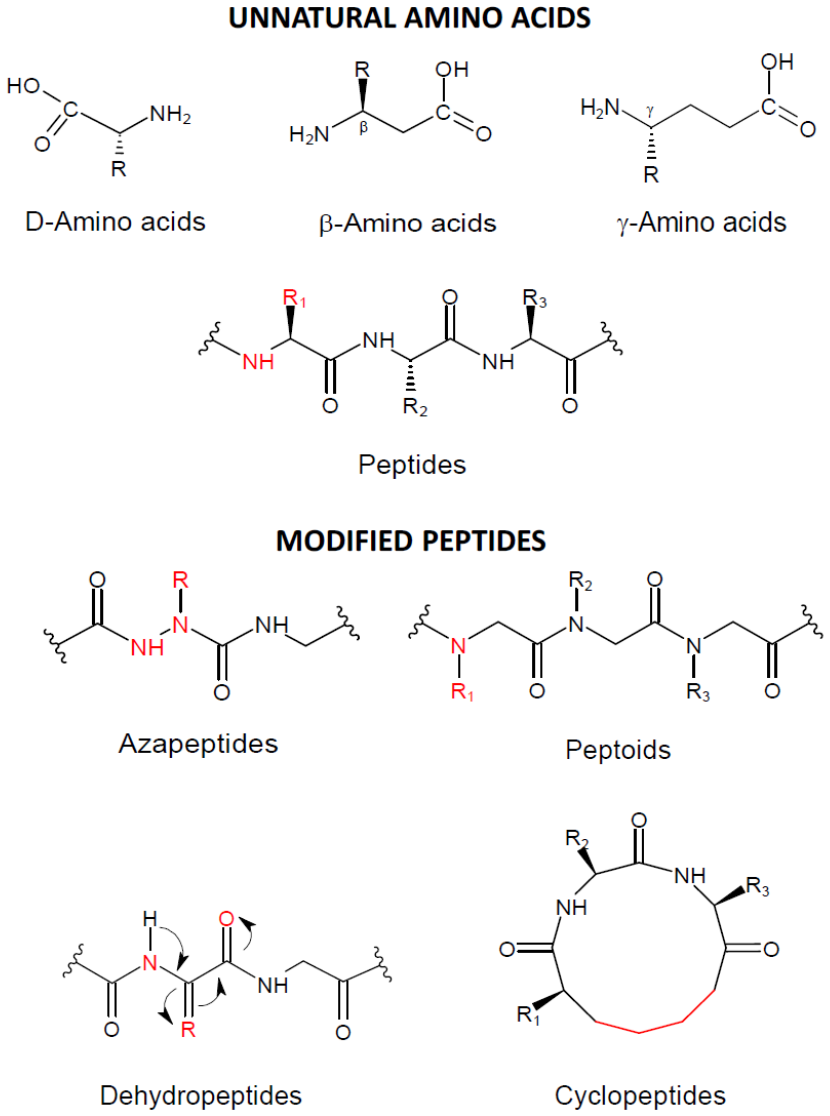
C. albicans selectively captures the fluorescently labelled C-terminal fragment of the Pra1 zincophore (AF647-SHQHTDSNPSATTDANSHCHTHADGEVHC)



Malavia, Łoboda, Wilson, Rowińska-Żyrek, in preparation

How to use this knowledge?

- In a rational design of novel AMP-metal complexes with **enhanced features which contibute to their antimicrobial efficiency**
- By attaching AMP complexes to commercially used drugs or appropriately designed **targeting domains**
- In a rational design of novel AMP-metal complexes with **enhanced proteolytic stability** (by using unnatural amino acids)



How to enhance the stability of therapeutic AMPs? The „retro-inverso” strategy

VFHLLGKIIHHVGNFVYGFSHVF	clavanin C native sequence
vfhllgkiihhvgnfvygfshvf	D-amino acid based clavanin C sequence
fvhsfgyvfngvhhiikgllhfv	retro-inverso clavanin C

The N-terminal part of clavanin C is marked in red; the C-terminal one – in violet.
L-amino acids are in capitals, D-amino acids – in small letters

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Wrocław University of Science and Technology

Robert Wieczorek

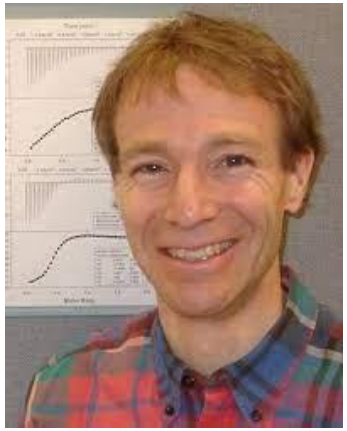
Tomasz Janek

Agnieszka Matera-Witkiewicz

Joanna Olesiak-Bańska

Danuta Witkowska
University of Opole, Poland

Dean Wilcox
Darmouth College, USA



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University of Balearic Islands

Miquel Barcelo-Oliver
University of Balearic Islands

Henryk Kozłowski
University of Opole, Poland

Duncan Wilson
University of Aberdeen, UK

Maurizio Remelli
University of Ferrara

Daniela Valensin
University of Siena

BAM

Biologically Active Metallopeptides

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