



Advances  
Against  
Aspergillosis &  
Mucormycosis

25<sup>th</sup>-27<sup>th</sup> January 2024

# Gliotoxin:

## Biosynthesis and biological activities

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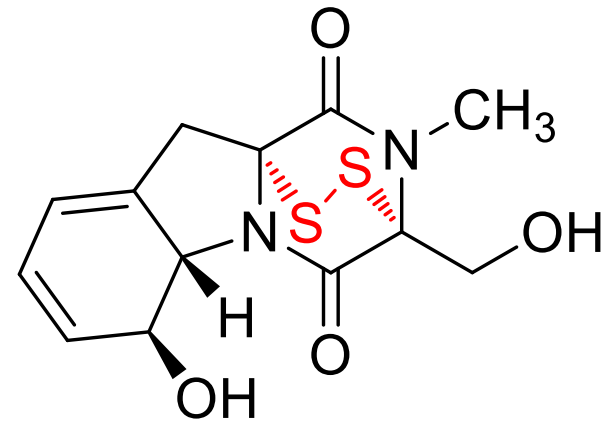


**THE FOURTH AFFILIATED HOSPITAL**  
**ZHEJIANG UNIVERSITY SCHOOL OF MEDICINE**

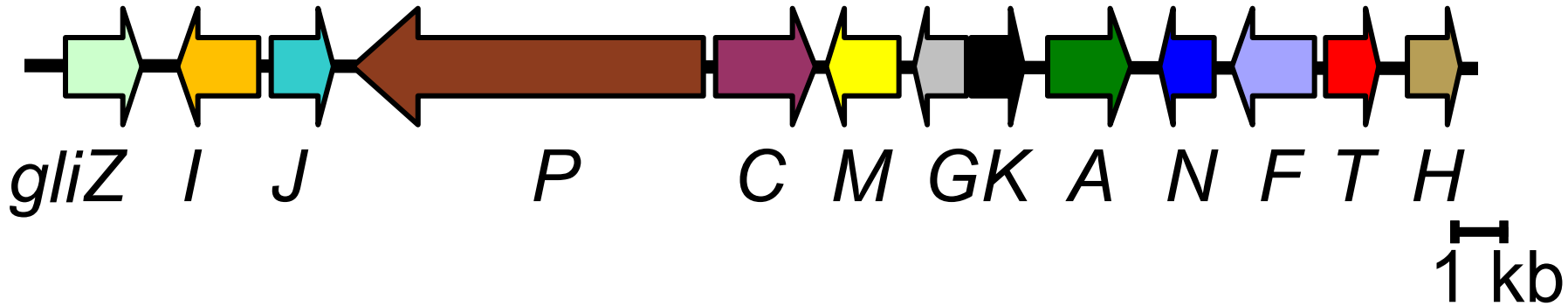
# Gliotoxin as an infamous mycotoxin

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- NRPS (nonribosomal peptide)
- ETP (epipolythiodioxopiperazine) type mycotoxin
- unique bioactive disulfide bridge
- ETPs are produced by various fungi (*Aspergillus fumigatus*, *Magnaporthe grisea*, *Leptosphaeria maculans*)



# Gliotoxin gene cluster



zinc finger Bok JW. *et al.*

amino cyclopropane carboxylate synthases

dipeptidase domain

non-ribosomal peptide synthetase Kupfahl C. *et al.*

cytochrome P450 monooxygenase

O-Methyl transferase domain

glutathione S-transferase domain

gamma-glutamyl transferase

transporter

methyl transferase domain

cytochrome P450 monooxygenase

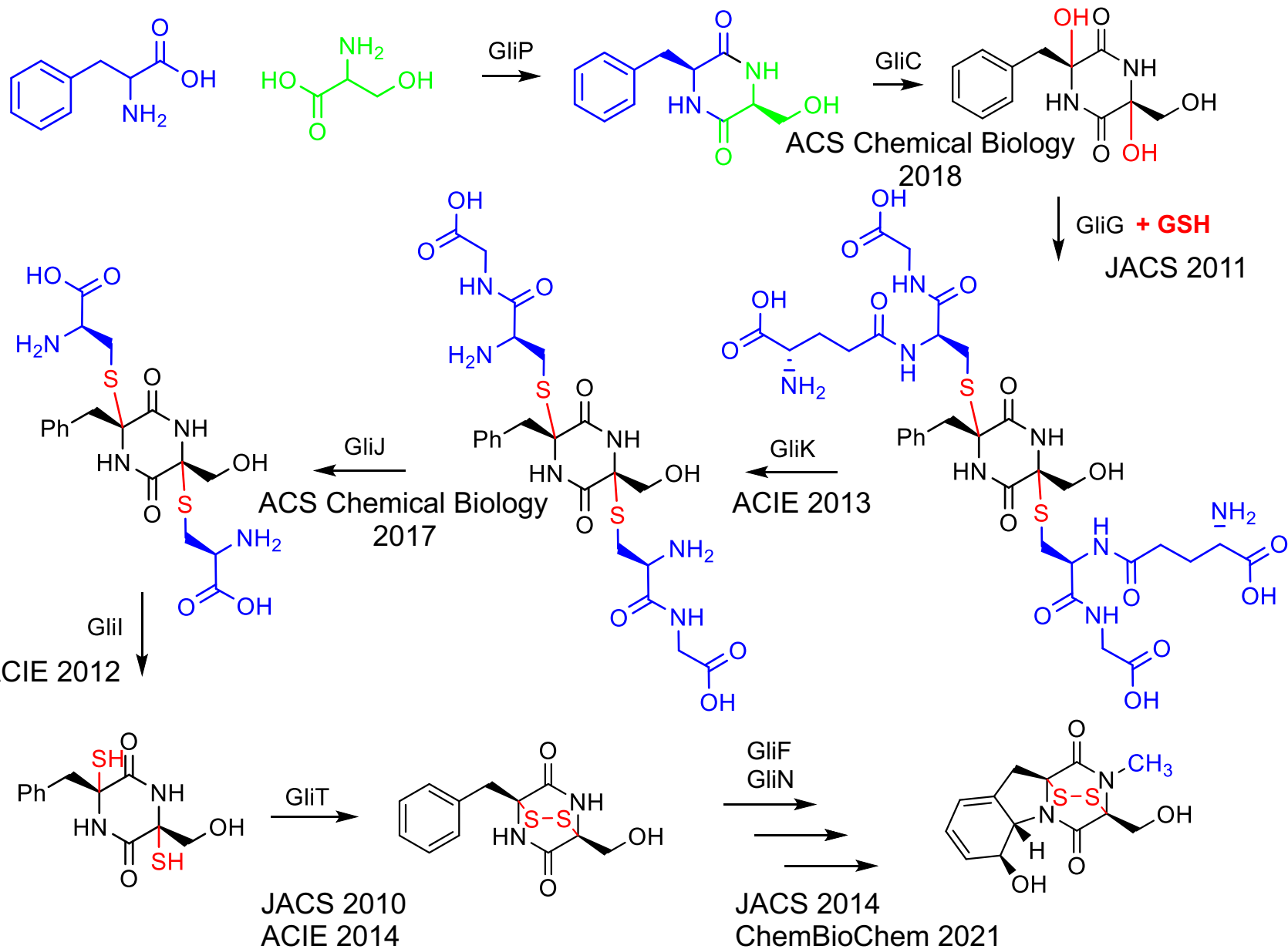
thioredoxin reductase

acetyl transferase

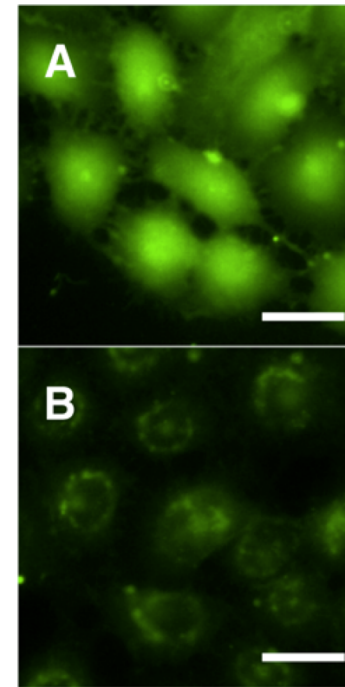
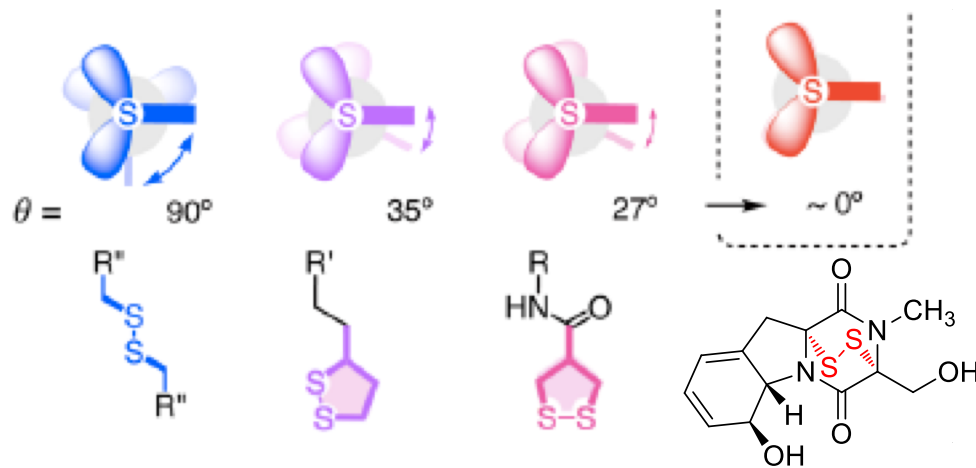
Gardiner DM, Waring P, Howlett BJ. Microbiology

Schrettl M *et al.* PLOS Pathogens

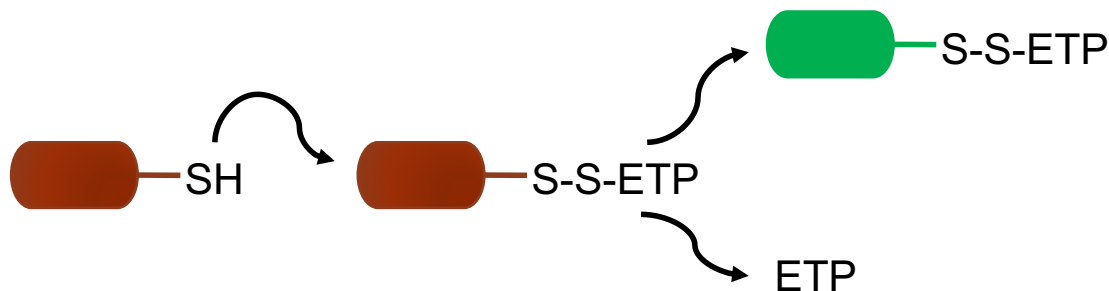
# Gliotoxin biosynthesis pathway



# Thiol-mediated cellular uptake



+ETP



Redox hopping mechanism

- Insensitive to inhibitors
- Highly efficient

Epidithiodiketopiperazines: Strain-Promoted Thiol-Mediated Cellular Uptake at the Highest Tension Zong L *et al.* ACS Cent Sci 2017

# Glutathione activities

## Redox cycling

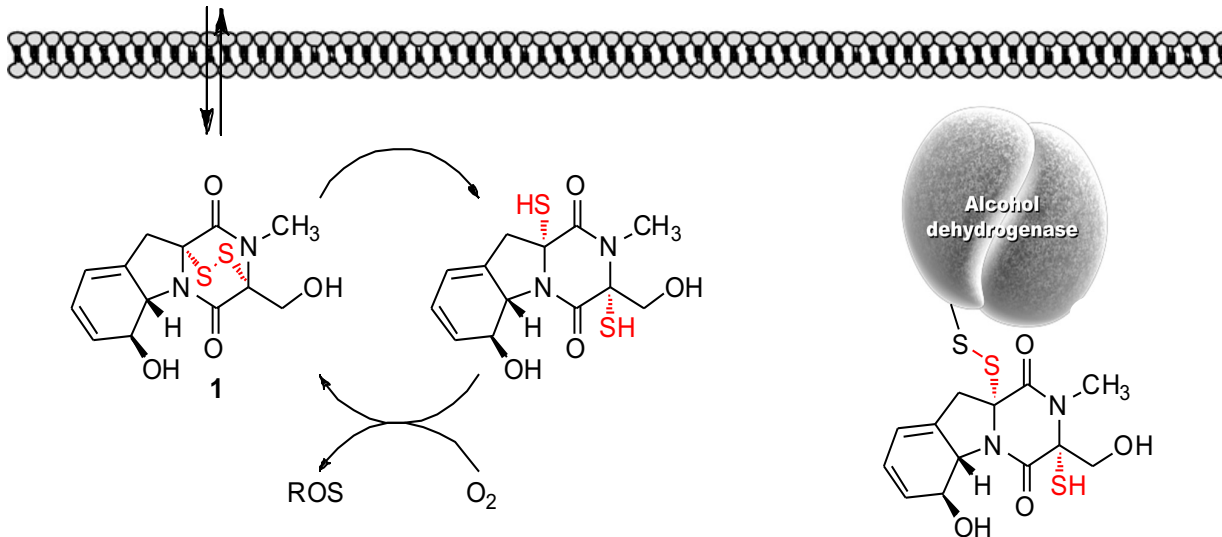
- Disruption of mitochondrial membrane potential
- Oxidation of biomolecules

## Formation of mixed disulfides

- Inhibition/Alteration of proteins e.g. proteasome, Bak, actin, etc.

## Metal chelation

- chelate  $Zn^{2+}$
- inhibits metalloenzymes



# Gliotoxin and *Aspergillus fumigatus* virulence

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Gliotoxin is a virulence factor of *Aspergillus fumigatus*: *gliP* deletion attenuates virulence in mice immunosuppressed with hydrocortisone Eukaryot Cell 2007

- loss of gliotoxin production has an effect on virulence in mice immunosuppressed with cortisone acetate

GliZ, a transcriptional regulator of gliotoxin biosynthesis, contributes to *Aspergillus fumigatus* virulence. Infect. Immun. 2006

Disruption of a nonribosomal peptide synthetase in *Aspergillus fumigatus* eliminates gliotoxin production. Eukaryot. Cell. 2006

Deletion of the *gliP* gene of *Aspergillus fumigatus* results in loss of gliotoxin production but has no effect on virulence of the fungus in a low-dose mouse infection model. Mol. Microbiol. 2006

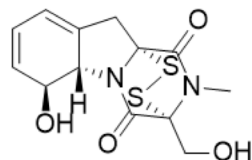
- no effect in low-dose model with neutropenic mice

Gliotoxin, a Known Virulence Factor in the Major Human Pathogen *Aspergillus fumigatus*, Is Also Biosynthesized by Its Nonpathogenic Relative *Aspergillus fischeri*. mBio. 2020

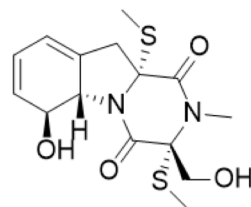
- loss of secondary metabolite production in *A. fischeri* has no impact on virulence

# Gliotoxin as diagnostic marker

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gliotoxin



bisdethiobis(methylthio)gliotoxin

Gliotoxin and bis(methylthio)gliotoxin are not reliable as biomarkers of invasive aspergillosis. *Mycoses* 2019

- bmGT was only detected in serum from one patient (5.6%) of 18 patients
- GT was not detected

Clinical validity of bis(methylthio)gliotoxin for the diagnosis of invasive aspergillosis. *Appl. Microbiol. Biotechnol.* 2016

- high amounts of serum bmGT correlate with mortality and probable/proven IA

Bis(methyl)gliotoxin proves to be a more stable and reliable marker for invasive aspergillosis than gliotoxin and suitable for use in diagnosis. *Diagn. Microbiol. Infect. Dis.* 2012

- bmGT was present in 10 (53%) of 18 patients at risk of IA
- GT was only detected in 2 (10%) of them