Meccanismi di azione dei prodotti fitosanitari e basi genetiche e fisiologiche della resistenza

Fungicidi

Gullino M.L., Faretra F.
Agroinnova - Università di Torino,
DIBCA - Università di Bari

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A REVIEW

Clinical significance of emergence of bacterial antimicrobial resistance in the hospital environment

B. Cookson

Laboratory of Healthcare Associated Infection, Specialist and Reference Microbiology Division, Health Protection Agency and London School of Hygiene and Tropical Medicine, London, UK

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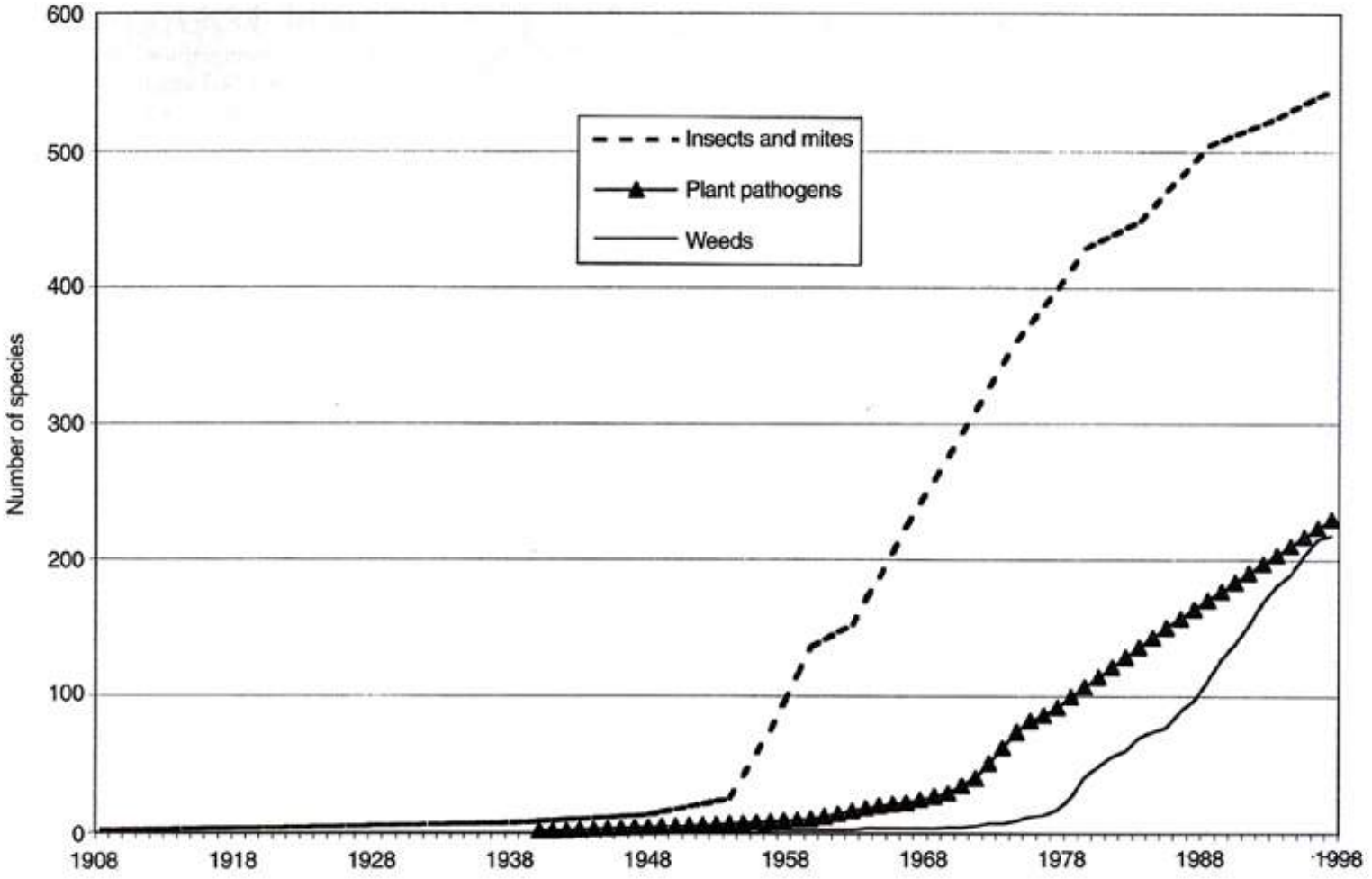
Resistenza a fungicidi

L’acquisizione di resistenza è un aspetto dell’adattabilità di una popolazione microbica al verificarsi di fattori avversi nell’ecosistema agrario, che ha la particolarità di essere aperto e fortemente influenzato dall’azione dell’uomo (Ciccarone, 1979)

Evoluzione storica



Number of pesticide-resistant species, 1908 to 1998.

Evoluzione dei fungicidi

- Era dello zolfo: dai tempi antichi (Omero, circa 1000 a.C.) al 1878
- Era del rame: dal 1878 al 1934
- Era dei fungicidi organici di sintesi: dal 1934 ai giorni nostri

Evoluzione dei fungicidi

- 1878: poltiglia bordolese (fungicida “universale”)
- 1910: ossicloruro tetraramico e, poco più tardi, ossicloruro di rame e calcio (Pasta e Polvere Caffaro)
- 1913: mercurioorganici (trattamento dei semi), derivati organici dell'arsenico
- 1931: ditiocarbammati (thiram o TMTD, ferbam e ziram)
- 1940: etilenbisditiocarbammati (nabam, zineb, maneb, mancozeb, ecc.)
- 1950: dinitrofenoli (dinocap)
- 1956: ftalimmidi (captan, folpet)
- 1959: guanidine (dodine)

Anni ‘60: fungicidi endoterapici/monosito

benzimidazoli, carbossianilidi, fenilammidi, IBS, dicarbossimidi, anilinopirimidine, fenexhamide, fenilpirroli, CAA, SDHI, QoI, QiI, QxI, ecc.

Vantaggi:

- Resistenza al dilavamento
- Potenziale azione curativa
- Ridistribuzione nella pianta
- Elevata attività biologica
- Efficacia a basse dosi
- Selettività
- Modesto impatto ambientale
- Bassa tossicità per l’uomo e gli animali

Svantaggi:

- Rischio di acquisizione di resistenza nei microrganismi bersaglio

Multisito

TARGET SITE AND CODE	GROUP NAME	CHEMICAL GROUP	COMMON NAME	COMMENTS	FRAC CODE
multi-site contact activity	inorganic	inorganic	copper (different salts)	Generally considered as a low risk group without any signs of resistance developing to the fungicides No cross resistance between group members M1 to M9	M1
	inorganic	inorganic	sulphur		M2
	dithiocarbamates and relatives	dithio-carbamates and relatives	ferbam mancozeb maneb metiram propineb thiram zineb ziram		M3
	phthalimides	phthalimides	captan captafol folpet		M4
	chloronitriles (phthalonitriles)	chloronitriles (phthalonitriles)	chlorothalonil		M5
	sulfamides	sulfamides	dichlofluanid tolylfluanid		M6
	guanidines	guanidines	guazatine iminoctadine		M7
	triazines	triazines	anilazine		M8
	quinones (anthraquinones)	quinones (anthra-quinones)	dithianon		M9

Non classificati

TARGET SITE AND CODE	GROUP NAME	CHEMICAL GROUP	COMMON NAME	COMMENTS	FRAC CODE
unknown	Diverse	diverse	mineral oils, organic oils, potassium bicarbonate, material of biological origin	Resistance not known	NC

P: Induttori difesa della pianta

TARGET SITE AND CODE	GROUP NAME	CHEMICAL GROUP	COMMON NAME	COMMENTS	FRAC CODE
P1: salicylic acid pathway	benzo-thiadiazole BTH	benzo-thiadiazole BTH	acibenzolar-S-methyl	Resistance not known	P
P2	benzisothiazole	benzisothiazole	probenazole (also antibacterial and antifungal activity)	Resistance not known	
P3	thiadiazole-carboxamide	thiadiazole-carboxamide	tiadinil isotianil	Resistance not known	
P4	natural compound	Polysaccharides	laminarin	Resistance not known	
P5	plant extract	complex mixture, ethanol extract	extract from *Reynoutria sachalinensis* (giant knotweed)	Resistance not known	

A: Sintesi di acidi nucleici

TARGET SITE AND CODE	GROUP NAME	CHEMICAL GROUP	COMMON NAME	COMMENTS	FRAC CODE
A1: RNA polymerase I	**PA** – fungicides (**P**henyl**A**mides)	acylalanines	benalaxyl benalaxyl-M (=kiralaxyl) furalaxyl metalaxyl metalaxyl-M (=mefenoxam)	Resistance and cross resistance well known in various Oomycetes but mechanism unknown. **High risk.** **See FRAC Phenylamide Guidelines for resistance management**	**4**
		oxazolidinones	oxadixyl		
		butyrolactones	ofurace		
A2: adenosin-deaminase	hydroxy-(2-amino-) pyrimidines	hydroxy-(2-amino-) pyrimidines	bupirimate dimethirimol ethirimol	Medium risk Resistance and cross resistance known in powdery mildews. Resistance management required.	**8**
A3: DNA/RNA synthesis (proposed)	heteroaromatics	isoxazoles	hymexazole	Resistance not known.	**32**
		isothiazolones	octhilinone		
A4: DNA topoisomerase type II (gyrase)	carboxylic acids	carboxylic acids	oxolinic acid	Bactericide. Resistance known. Risk in fungi unknown. Resistance management required.	**31**

B: Mitosi e divisione cellulare

TARGET SITE AND CODE	GROUP NAME	CHEMICAL GROUP	COMMON NAME	COMMENTS	FRAC CODE
B1: ß-tubuline assembly in mitosis	**MBC** - fungicides (**M**ethyl **B**enzimidazole **C**arbamates)	benzimidazoles	benomyl carbendazim fuberidazole thiabendazole	Resistance common in many fungal species. Several target site mutations, mostly E198A/G/K, F200Y in β-tubulin gene.	1
		thiophanates	thiophanate thiophanate-methyl	Positive cross resistance between the group members. Negative cross resistance to N-Phenylcarbamates. **High risk. See FRAC Benzimidazole Guidelines for resistance management.**	
B2: ß-tubulin assembly in mitosis	N-phenyl carbamates	N-phenyl carbamates	diethofencarb	Resistance known. Target site mutation E198K. Negative cross resistance to benzimidazoles. High risk. Resistance management required.	10
B3: ß-tubulin assembly in mitosis	benzamides	Toluamides	zoxamide	Low to medium risk. Resistance management required.	22
B4: cell division (proposed)	phenylureas	Phenylureas	pencycuron	Resistance not known	20
B5: delocalisation of spectrin-like proteins	benzamides	pyridinylmethyl-benzamides	fluopicolide	Resistance not known	43

C: Respirazione (1/3)

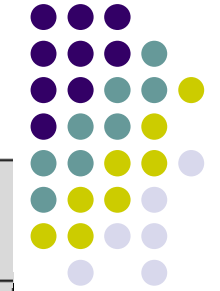
TARGET SITE AND CODE	GROUP NAME	CHEMICAL GROUP	COMMON NAME	COMMENTS	FRAC CODE
C1: complex I NADH Oxido-reductase	pyrimidinamines	pyrimidinamines	diflumetorim	Resistance not known.	**39**
C2: complex II: succinate-dehydro-genase	SDHI (**S**uccinate **dehydrogenase** **i**nhibitors)	phenyl-benzamides	benodanil flutolanil mepronil	Resistance known for several fungal species in field populations and lab mutants. Target site mutations in sdh gene, e.g. H/Y (or H/L) at 257, 267, 272 or P225L, dependent on fungal species. Resistance management required. **Medium to high risk.** **See FRAC SDHI Guidelines for resistance management.**	**7**
		pyridinyl-ethyl-benzamides	fluopyram		
		furan- carboxamides	fenfuram		
		oxathiin-carboxamides	carboxin oxycarboxin		
		thiazole-carboxamides	thifluzamide		
		pyrazole-carboxamides	benzovindiflupyr bixafen fluxapyroxad furametpyr isopyrazam penflufen penthiopyrad sedaxane		
		pyridine-carboxamides	boscalid		

C: Respirazione (2/3)

TARGET SITE AND CODE	GROUP NAME	CHEMICAL GROUP	COMMON NAME	COMMENTS	FRAC CODE
C3: complex III: cytochrome bc1 (ubiquinol oxidase) at Qo site *(cyt b gene)*	**QoI**-fungicides (**Q**uinone **o**utside **I**nhibitors)	methoxy-acrylates	azoxystrobin coumoxystrobin enoxastrobin flufenoxystrobin picoxystrobin pyraoxystrobin	Resistance known in various fungal species. Target site mutations in cyt b gene (G143A, F129L) and additional mechanisms. Cross resistance shown between all members of the QoI group. **High risk.** **See FRAC QoI Guidelines for resistance management.**	11
		methoxy-carbamates	pyraclostrobin pyrametostrobin triclopyricarb		
		oximino acetates	kresoxim-methyl trifloxystrobin		
		oximino-acetamides	dimoxystrobin fenaminostrobin metominostrobin orysastrobin		
		oxazolidine-diones	famoxadone		
		dihydro-dioxazines	fluoxastrobin		
		Imidazolinones	fenamidone		
		benzyl-carbamates	pyribencarb		
C4: complex III: cytochrome bc1(ubiquinone reductase) at Qi site	**QiI** - fungicides (**Q**uinone **i**nside **I**nhibitors)	cyano- imidazole	cyazofamid	Resistance risk unknown but assumed to be medium to high (mutations at target site known in model organisms). Resistance management required.	21
		sulfamoyl-triazole	amisulbrom		

C: Respirazione (3/3)

TARGET SITE AND CODE	GROUP NAME	CHEMICAL GROUP	COMMON NAME	COMMENTS	FRAC CODE
C5: uncouplers of oxidative phos-phorylation		dinitrophenyl crotonates	binapacryl meptyldinocap dinocap	Resistance not known. Also acaricidal activity.	29
		2,6-dinitro-Anilines	fluazinam	Low risk. However, resistance claimed in *Botrytis* in Japan.	
		(Pyr.-hydrazones)	(Ferimzone)	Reclassified to U 14 in 2012.	
C6: inhibitors of oxidative phos-phorylation, ATP synthase	organo tin compounds	tri phenyl tin compounds	fentin acetate fentin chloride fentin hydroxide	Some resistance cases known. Low to medium risk.	30
C7: ATP production (proposed)	thiophene-carboxamides	thiophene-carboxamides	silthiofam	Resistance reported. Risk low.	38
C8: complex III: cytochrome bc1 (ubiquinone reductase) at Q x (unknown) site	QxI – fungicide (Quinone x Inhibitor)	triazolo-pyrimidylamine	ametoctradin	Resistance risk assumed to be medium to high (single site inhibitor). Resistance management required.	45



D: Sintesi aminoacidi/proteine

TARGET SITE AND CODE	GROUP NAME	CHEMICAL GROUP	COMMON NAME	COMMENTS	FRAC CODE
D1: methionine biosynthesis (proposed) *(cgs gene)*	**AP -** fungicides (**A**nilino-**P**yrimidines)	anilino-pyrimidines	cyprodinil mepanipyrim pyrimethanil	Resistance known in *Botrytis* and *Venturia*, sporadically in *Oculimacula* . **Medium risk. See FRAC Anilinopyrimidine Guidelines for resistance management.**	**9**
D2: protein synthesis	enopyranuronic acid antibiotic	enopyranuronic acid antibiotic	blasticidin-S	Low to medium risk. Resistance management required.	**23**
D3: protein synthesis	hexopyranosyl antibiotic	hexopyranosyl antibiotic	kasugamycin	Resistance known in fungal and bacterial (*P. glumae*) pathogens. Medium risk. Resistance management required.	**24**
D4: protein synthesis	glucopyranosyl antibiotic	glucopyranosyl antibiotic	streptomycin	Bactericide. Resistance known. High risk. Resistance management required.	**25**
D5: protein synthesis	tetracycline antibiotic	tetracycline antibiotic	oxytetracycline	Bactericide. Resistance known. High risk. Resistance management required.	**41**

E: Trasduzione del segnale

TARGET SITE AND CODE	GROUP NAME	CHEMICAL GROUP	COMMON NAME	COMMENTS	FRAC CODE
E1: Signal transduction (mechanism unknown)	aza-naphthalenes	aryloxyquinoline	quinoxyfen	Resistance to quinoxyfen known. Medium risk. Resistance management required. Cross resistance found in *Erysiphe (Uncinula) necator* but not in *Blumeria graminis*.	**13**
		Quinazolinone	proquinazid		
E2: MAP/Histidine-Kinase in osmotic signal transduction *(os-2, HOG1)*	**PP**-fungicides (**P**henyl**P**yrroles)	Phenylpyrroles	fenpiclonil fludioxonil	Resistance found sporadically, mechanism speculative. Low to medium risk. Resistance management required.	**12**
E3: MAP/Histidine-Kinase in osmotic signal transduction *(os-1, Daf1)*	dicarboximides	dicarboximides	chlozolinate iprodione procymidone vinclozolin	Resistance common in *Botrytis* and some other pathogens. Several mutations in OS-1, mostly I365S. Cross resistance common between the group members. **Medium to high risk. See FRAC Dicarboximide Guidelines for resistance management.**	**2**

F: Sintesi lipidi e integrità membrane

TARGET SITE AND CODE	GROUP NAME	CHEMICAL GROUP	COMMON NAME	COMMENTS	FRAC CODE
F1:	formerly dicarboximides				
F2: phospholipid biosynthesis, methyltrans-ferase	phosphoro-thiolates	phosphoro-thiolates	edifenphos iprobenfos (IBP) pyrazophos	Resistance known in specific fungi. Low to medium risk. Resistance management required if used for risky pathogens.	**6**
	dithiolanes	Dithiolanes	isoprothiolane		
F3: lipid peroxidation (proposed)	**AH**-fungicides (**A**romatic **H**ydrocarbons) (chlorophenyls, nitroanilines)	aromatic hydrocarbons	biphenyl chloroneb dicloran quintozene (PCNB) tecnazene (TCNB) tolclofos-methyl	Resistance known in some fungi. Low to medium risk. Cross resistance patterns complex due to different activity spectra.	**14**
	heteroaromatics	1,2,4-thiadiazoles	etridiazole		
F4: cell membrane permeability, fatty acids (proposed)	carbamates	Carbamates	iodocarb propamocarb prothiocarb	Low to medium risk. Resistance management required.	**28**
F5:	**formerly CAA**-fungicides				
F6: microbial disrupters of pathogen cell membranes	Microbial (*Bacillus* sp.)	*Bacillus subtilis* and the fungicidal lipopeptides produced	*Bacillus subtilis* strain QST 713	Resistance not known.	**44**
			Bacillus subtilis strain FZB24	Induction of host plant defence described as additional mode of action for strain FZB24	
F7: cell membrane disruption (proposed)	plant extract	terpene hydrocarbons and terpene alcohols	extract from *Melaleuca alternifolia* (tea tree)	Resistance not known	**46**

G: Biosintesi steroli (1/2)

TARGET SITE AND CODE	GROUP NAME	CHEMICAL GROUP	COMMON NAME	COMMENTS	FRAC CODE
G1: C14- demethylase in sterol biosynthesis *(erg11/cyp51)*	**DMI**-fungicides (**DeM**ethylation **I**nhibitors) (SBI: Class I)	piperazines	triforine	There are big differences in the activity spectra of DMI fungicides. Resistance is known in various fungal species. Several resistance mechanisms are known incl. target site mutations in cyp51 (erg 11) gene, e.g. V136A, Y137F, A379G, I381V; cyp51 promotor; ABC transporters and others. Generally wise to accept that cross resistance is present between DMI fungicides active against the same fungus. DMI fungicides are Sterol Biosynthesis Inhibitors (SBIs), but show no cross resistance to other SBI classes. **Medium risk.** **See FRAC SBI Guidelines for resistance management.**	**3**
		pyridines	pyrifenox pyrisoxazole		
		pyrimidines	fenarimol nuarimol		
		imidazoles	imazalil oxpoconazole pefurazoate prochloraz triflumizole		
		triazoles	azaconazole bitertanol bromuconazole cyproconazole difenoconazole diniconazole epoxiconazole etaconazole fenbuconazole fluquinconazole flusilazole flutriafol hexaconazole imibenconazole ipconazole metconazole myclobutanil penconazole propiconazole simeconazole tebuconazole tetraconazole triadimefon triadimenol triticonazole		
		triazolinthiones	prothioconazole		

G: Biosintesi steroli (2/2)

TARGET SITE AND CODE	GROUP NAME	CHEMICAL GROUP	COMMON NAME	COMMENTS	FRAC CODE
G2: Δ^{14}-reductase and $\Delta^{8}\rightarrow\Delta^{7}$-isomerase in sterol biosynthesis *(erg24, erg2)*	Amines ("Morpholines") (SBI: Class II)	morpholines	aldimorph dodemorph fenpropimorph tridemorph	Decreased sensitivity for powdery mildews. Cross resistance within the group generally found but not to other SBI classes. **Low to medium risk. See FRAC SBI Guidelines for resistance management.**	**5**
		piperidines	fenpropidin piperalin		
		spiroketal-amines	spiroxamine		
G3: 3-keto reduc-tase, C4- de-methylation *(erg27)*	hydroxyanilides (SBI: Class III)	hydroxyanilides	fenhexamid	Low to medium risk. Resistance management required.	**17**
G4: squalene-epoxidase in sterol biosynthesis *(erg1)*	(SBI class IV)	thiocarbamates	pyributicarb	Resistance not known, fungicidal and herbicidal activity	**18**
		allylamines	naftifine terbinafine	Medical fungicides only	

H: Biosintesi parete cellulare

TARGET SITE AND CODE	GROUP NAME	CHEMICAL GROUP	COMMON NAME	COMMENTS	FRAC CODE
H3: trehalase and inositol-biosynthesis	glucopyranosyl antibiotic	glucopyranosyl antibiotic	validamycin	Resistance not known	**26**
H4: chitin synthase	polyoxins	peptidyl pyrimidine nucleoside	polyoxin	Resistance known. Medium risk. Resistance management required.	**19**
H5: cellulose synthase	**CAA**-fungicides (**C**arboxylic **A**cid **A**mides)	cinnamic acid amides	dimethomorph flumorph	Resistance known in *Plasmopara viticola* but not in *Phytophthora infestans*. Cross resistance between all members of the CAA group. **Low to medium risk. See FRAC CAA Guidelines for resistance management**	**40**
		valinamide carbamates	benthiavalicarb iprovalicarb valifenalate		
		mandelic acid amides	mandipropamid		

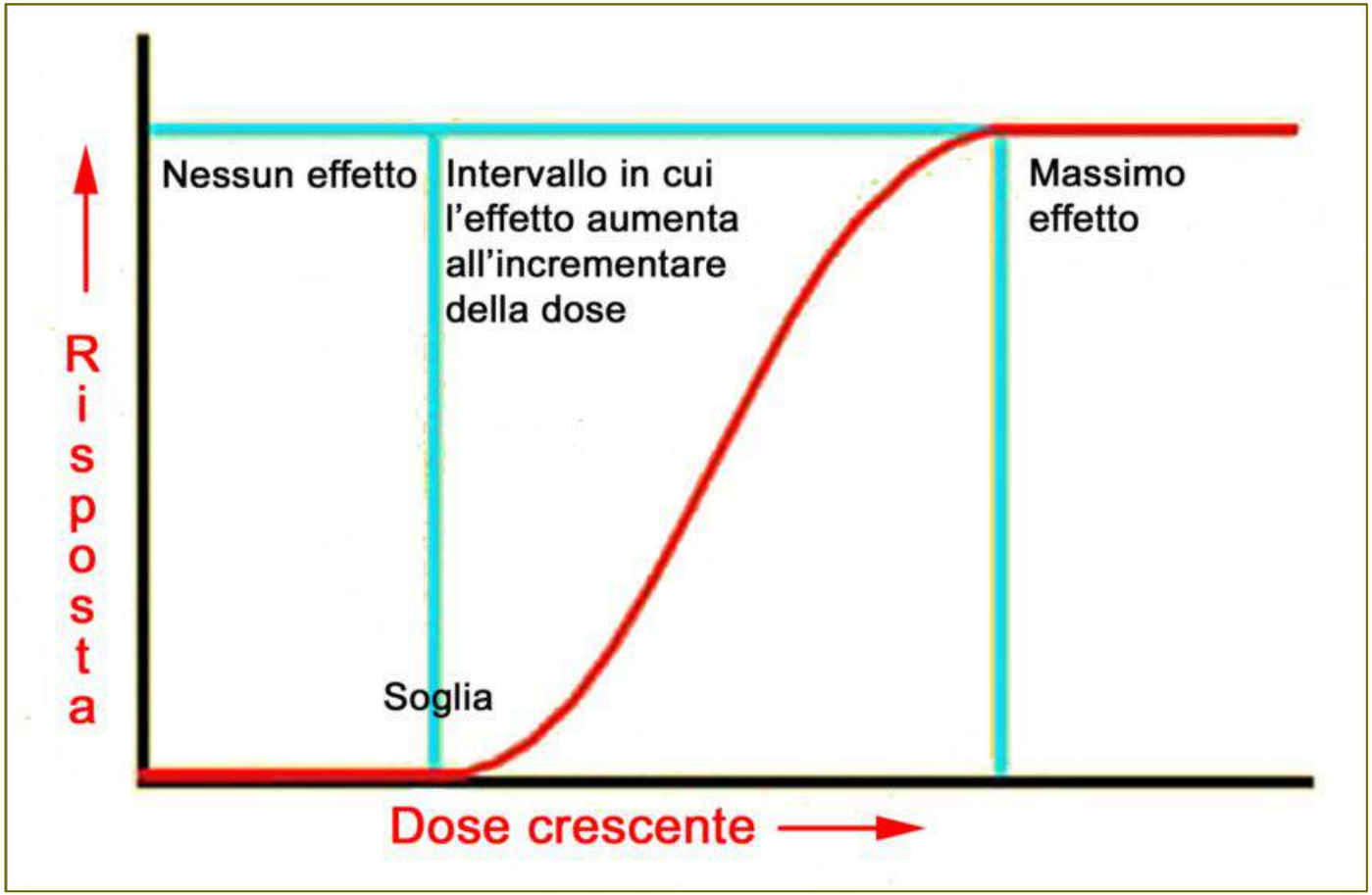
I: Sintesi melanina

TARGET SITE AND CODE	GROUP NAME	CHEMICAL GROUP	COMMON NAME	COMMENTS	FRAC CODE
I1: reductase in melanin biosynthesis	**MBI-R** (**M**elanin **B**iosynthesis **I**nhibitors – **R**eductase)	isobenzo-furanone	fthalide	Resistance not known	**16.1**
		pyrrolo-quinolinone	pyroquilon		
		triazolobenzo-thiazole	tricyclazole		
I2: dehydratase in melanin biosynthesis	**MBI-D** (**M**elanin **B**iosynthesis **I**nhibitors – **D**ehydratase)	cyclopropane-carboxamide	carpropamid	Resistance known. Medium risk. Resistance management required.	**16.2**
		carboxamide	diclocymet		
		propionamide	fenoxanil		

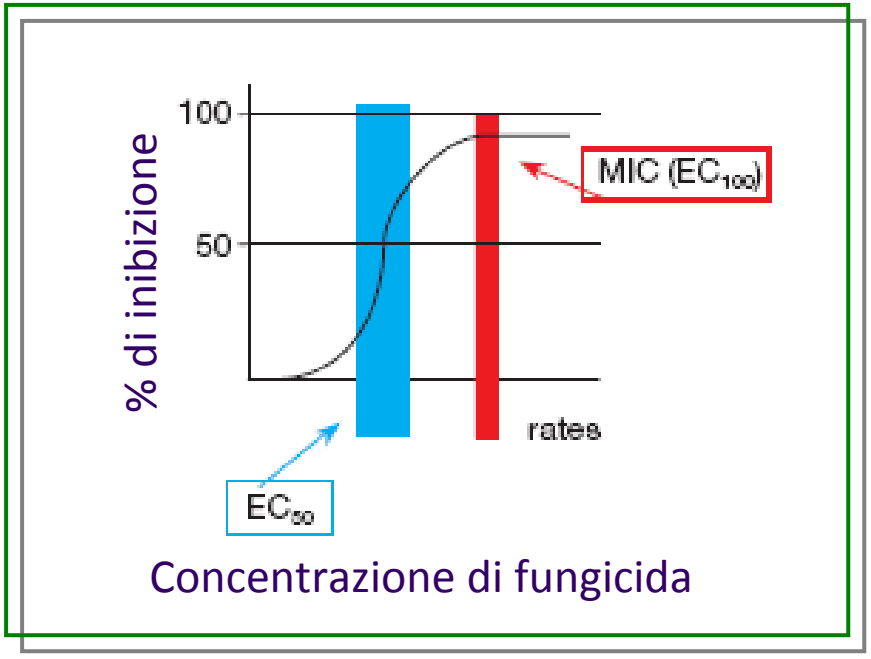
Meccanismo d’azione non noto

TARGET SITE AND CODE	GROUP NAME	CHEMICAL GROUP	COMMON NAME	COMMENTS	FRAC CODE
unknown	cyanoacetamide-oxime	cyanoacetamide-oxime	cymoxanil	Resistance claims described Low to medium risk. Resistance management required.	27
unknown	phosphonates	ethyl phosphonates	fosetyl Al	Few resistance cases reported in few pathogens. Low risk	33
			phophorous acid and salts		
unknown	phthalamic acids	phthalamic acids	teclofthalam (Bactericide)	Resistance not known	34
unknown	benzotriazines	benzotriazines	triazoxide	Resistance not known	35
unknown	benzene sulfonamides	benzene sulphonamides	flusulfamide	Resistance not known	36
unknown	pyridazinones	pyridazinones	diclomezine	Resistance not known	37
unknown	thiocarbamate	thiocarbamate	methasulfocarb	Resistance not known	42
microtubule disruption (proposed)	thiazole carboxamide	ethylamino-thiazole carboxamide	ethaboxam	Resistance not known	U5
unknown	phenyl-acetamide	phenyl-acetamide	cyflufenamid	Resistance in *Sphaerotheca* Resistance management required	U6
actin disruption (proposed)	aryl phenyl ketone	benzophenone	metrafenone	Less sensitive isolates detected in wheat powdery mildew. Medium risk Resistance management required.	U8
		benzoylpyridine	pyriofenone		
Cell membrane disruption (proposed)	Guanidines	guanidines	dodine	Resistance known in *Venturia inaequalis* Low to medium risk. Resistance management recommended.	U12
unknown	Thiazolidine	cyano methylene thiazolidine	flutianil	Resistance not known	U13
unknown	pyrimidinone-hydrazones	pyrimidinone-hydrazones	ferimzone	Resistance not known Reclassified from C5 in 2012	U14

Curve dose-risposta



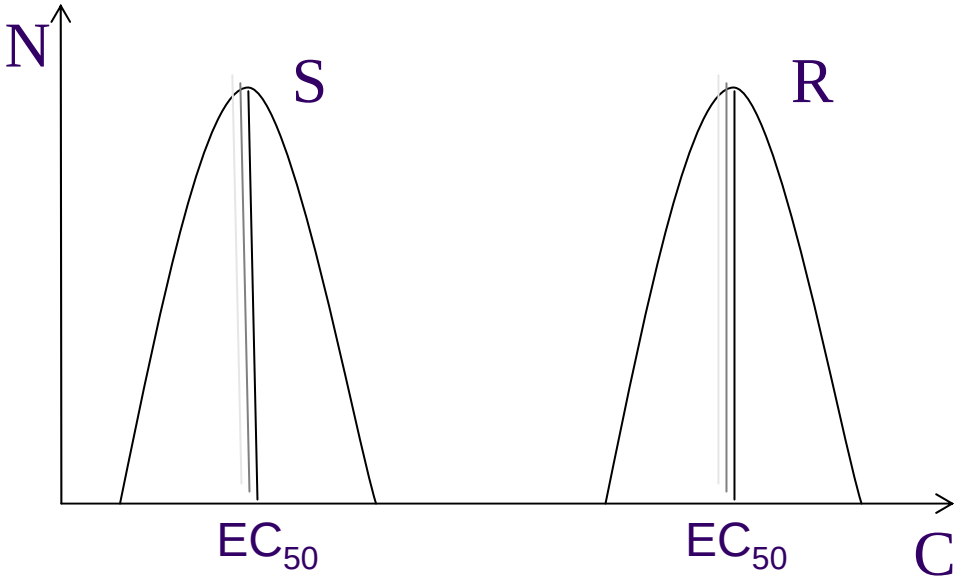
- EC_{50} (Concentrazione Efficace Mediana)
  - Concentrazione di fungicida in grado di inibire il 50% degli individui
- MIC (Minimum Inhibitory Concentration)
  - Concentrazione minima che determina l'inibizione di una popolazione



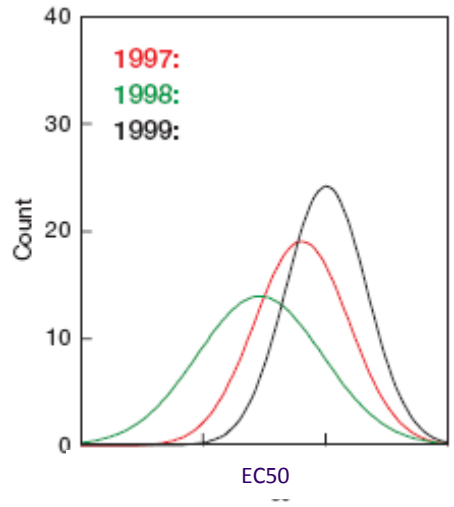
- Fattore di resistenza

$$FR = \frac{EC_{50}resistenti}{EC_{50}sensibili}$$

- Comparazione EC_{50} pregressi
  - Se disponibili (“baseline sensitivity”)



Es. *P. viticola* / fenamidone

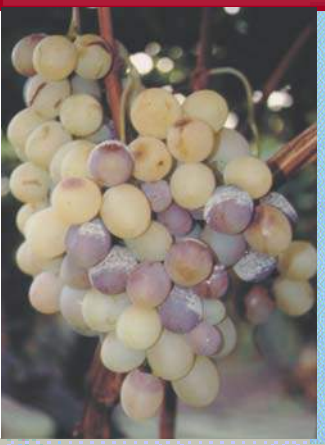


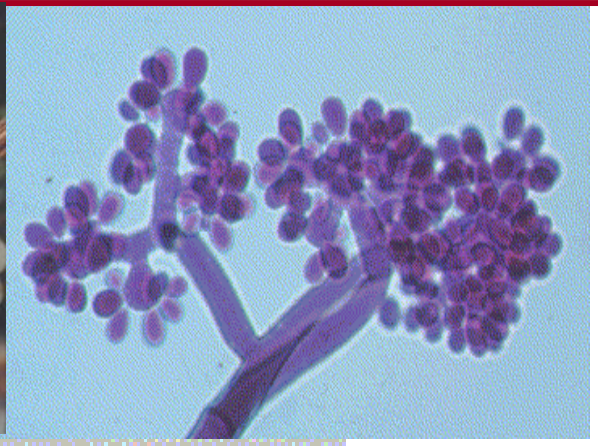
Distribuzione dei ceppi di *P. viticola* in funzione dell’EC_{50}

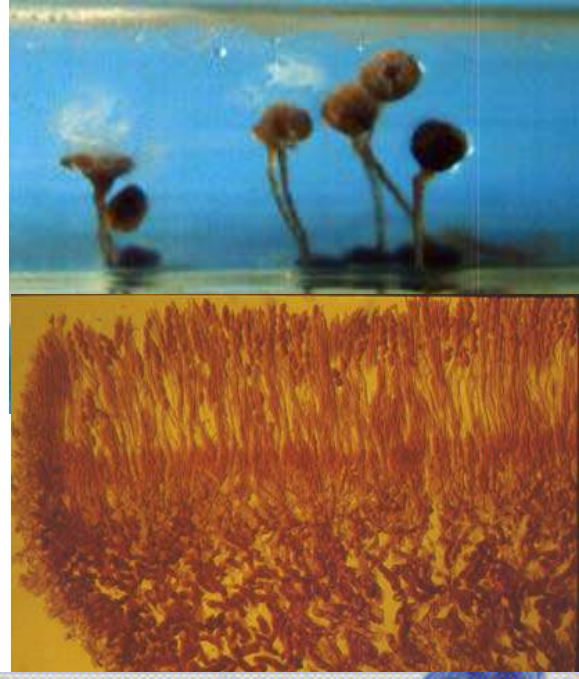
Basi genetiche

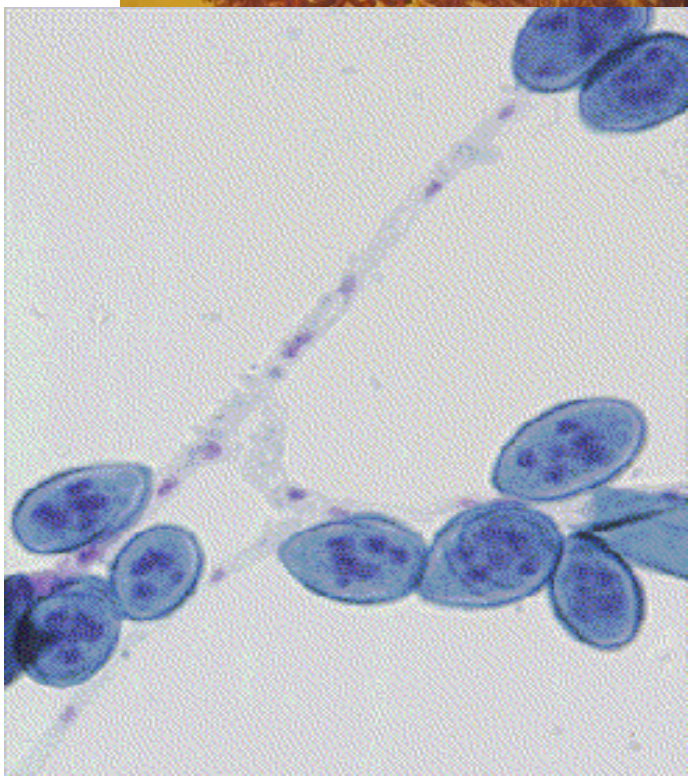
- Fenomeno genetico (carattere ereditabile)
- Immediatamente espressa in funghi aploidi, nei diploidi è governata dai rapporti di dominanza/recessività
- Geni nucleari (cromosomici) o determinanti genetici citoplasmatici (extracromosomici)
- Determinismo monogenico, oligogenico o poligenico
- Epistasi - geni modificatori
- Resistenza multiallelica

Fonti di variabilità





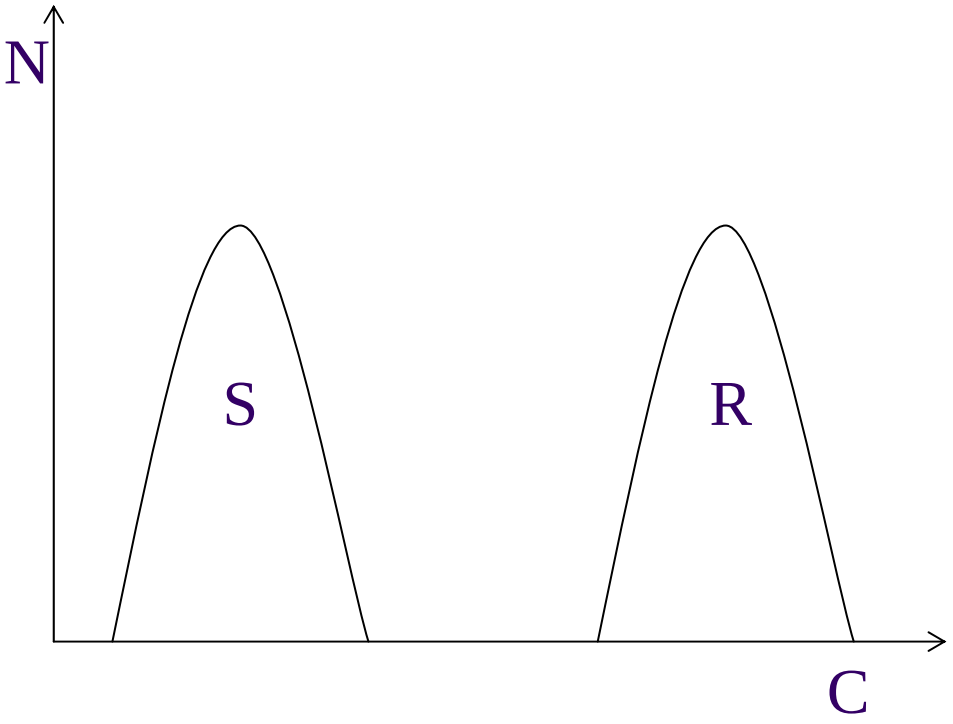


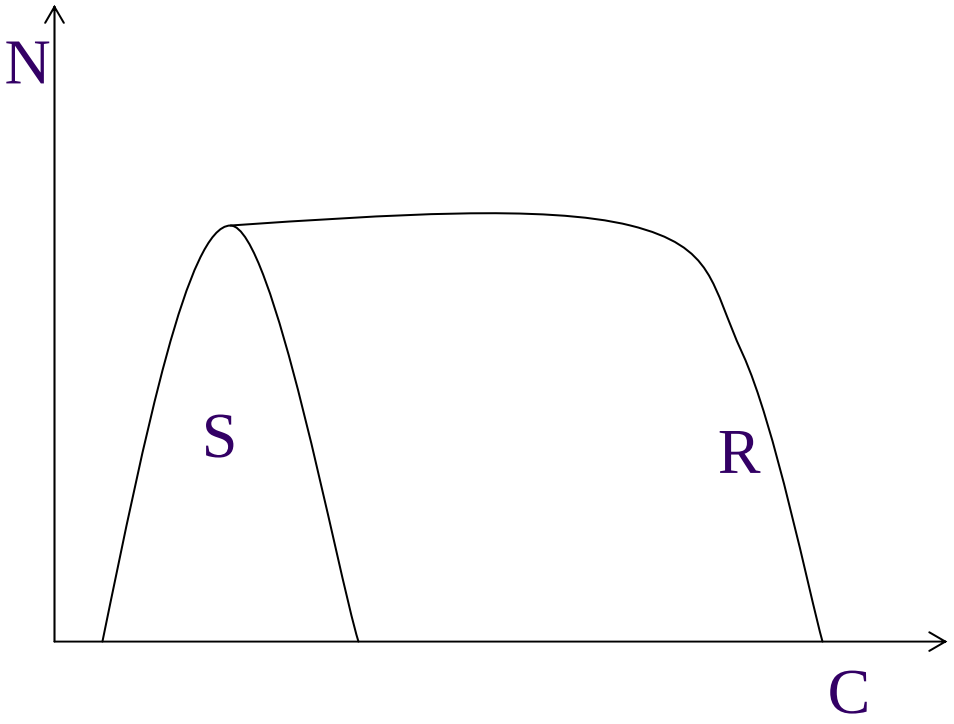


Basi genetiche

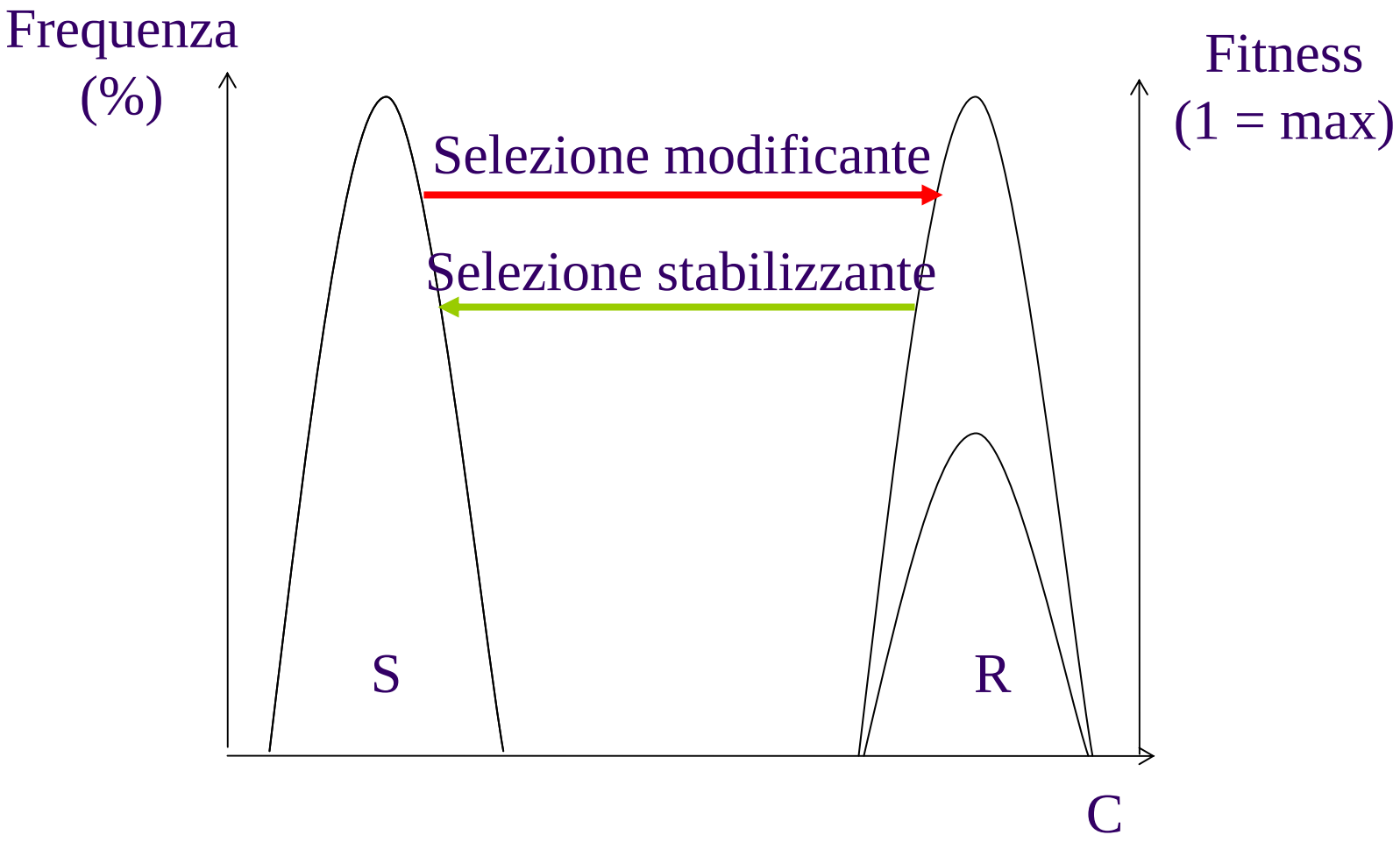
Resistenza monogenica

Resistenza poligenica

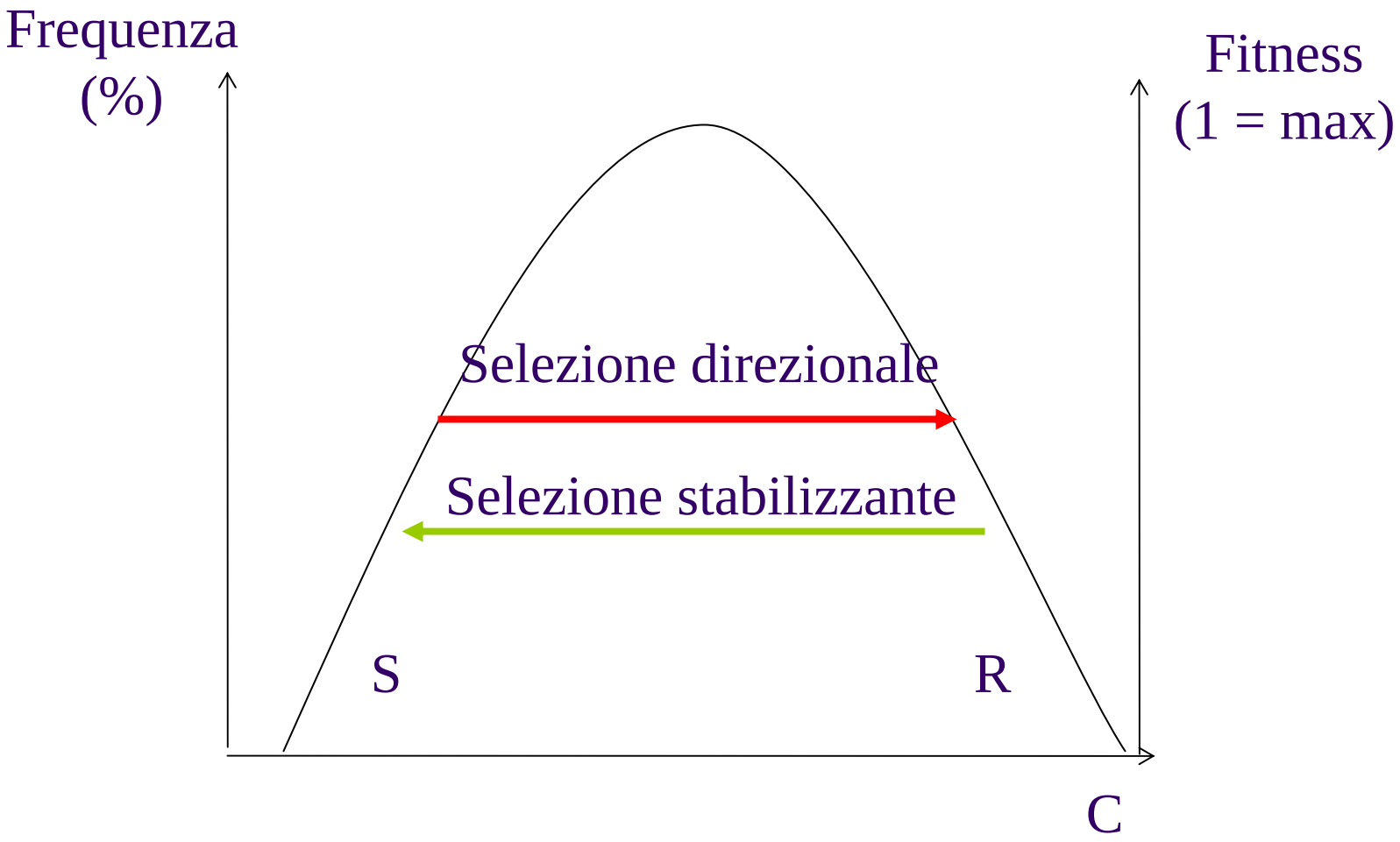




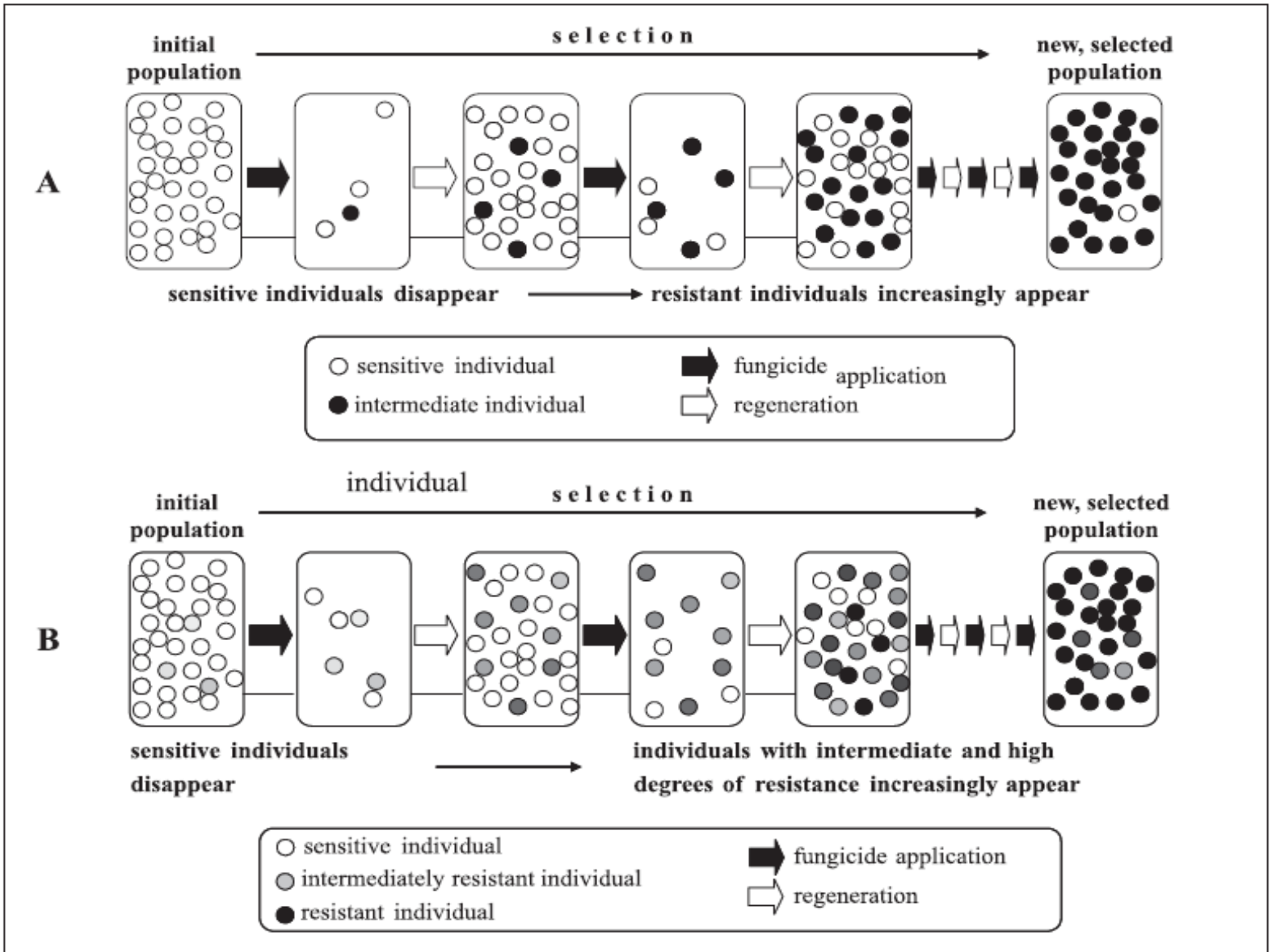
Genetica di popolazione

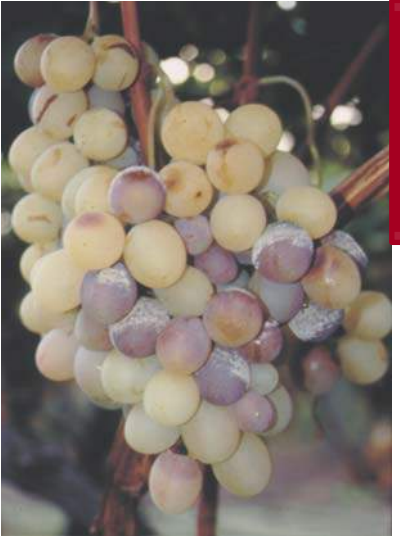


Genetica di popolazione



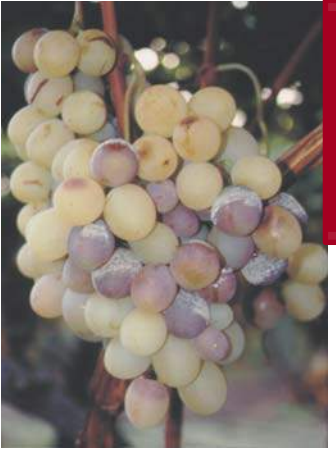
Genetica di popolazione





Resistenza multiallelica (*Mbc1*)

Benzimidazolici	Diethofencarb
S	NS
LR	NS
HR	IS
HR	NS



Resistenza multiallelica (*Daf1*)

Dicarbossimidici	Pressione osmotica	Fenilpirroli
S	+	S
LR	±	S
HR	-	S
HR	± → +	S
HR	-	LR
HR	-	HR

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Review

Advances in understanding molecular mechanisms of fungicide resistance and molecular detection of resistant genotypes in phytopathogenic fungi

Zhonghua Ma[1], Themis J. Michailides*

Department of Plant Pathology, Kearney Agricultural Center, University of California, Davis, 9240 South Riverbend Avenue, Parlier, CA 93648, USA

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Abstract

Although fungicide treatments are a key component in the integrated management of many plant diseases, the appearance of resistance has become an important factor in limiting the efficacy and useful lifetime of fungicides developed at increasingly higher costs. Extensive molecular studies have led to advances in our understanding of mechanisms of fungicide resistance and in developing effective, rapid methods for detection of resistant genotypes of pathogens. This paper reviews recent advances in our understanding of resistance mechanisms of phytopathogenic fungi to some major classes of fungicides (benzimidazoles, demethylation inhibitors [DMIs], Qo respiration inhibitors [QoIs], and dicarboximides [DCFs]) at a molecular level and developments in molecular detection of fungicide-resistant fungi.

Keywords: Benzimidazoles; Demethylation inhibitors (DMIs); Dicarboximides; Fungicide resistance; Qo respiration inhibitors (QoIs); Strobilurins

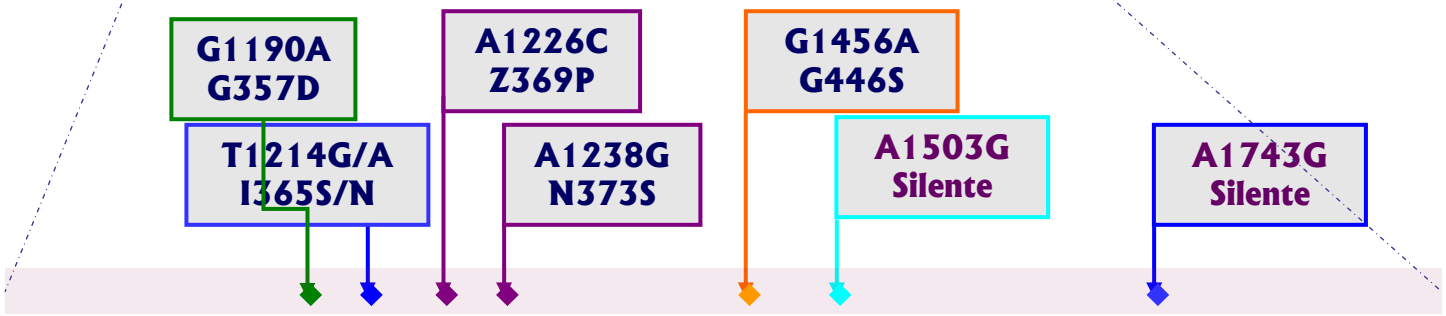
Daf1 gene (1197 bps)

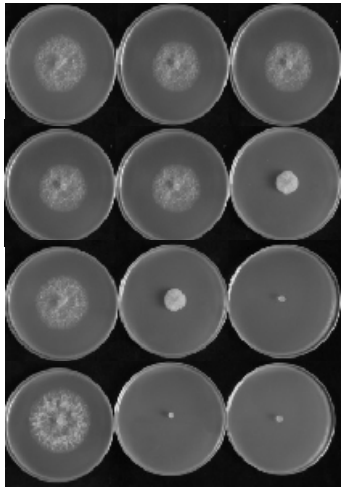
—: Introns

90 aa repeat domain

Kinase core domain

Response regulator domain





Daf1HR

Daf1MR

Daf1LR

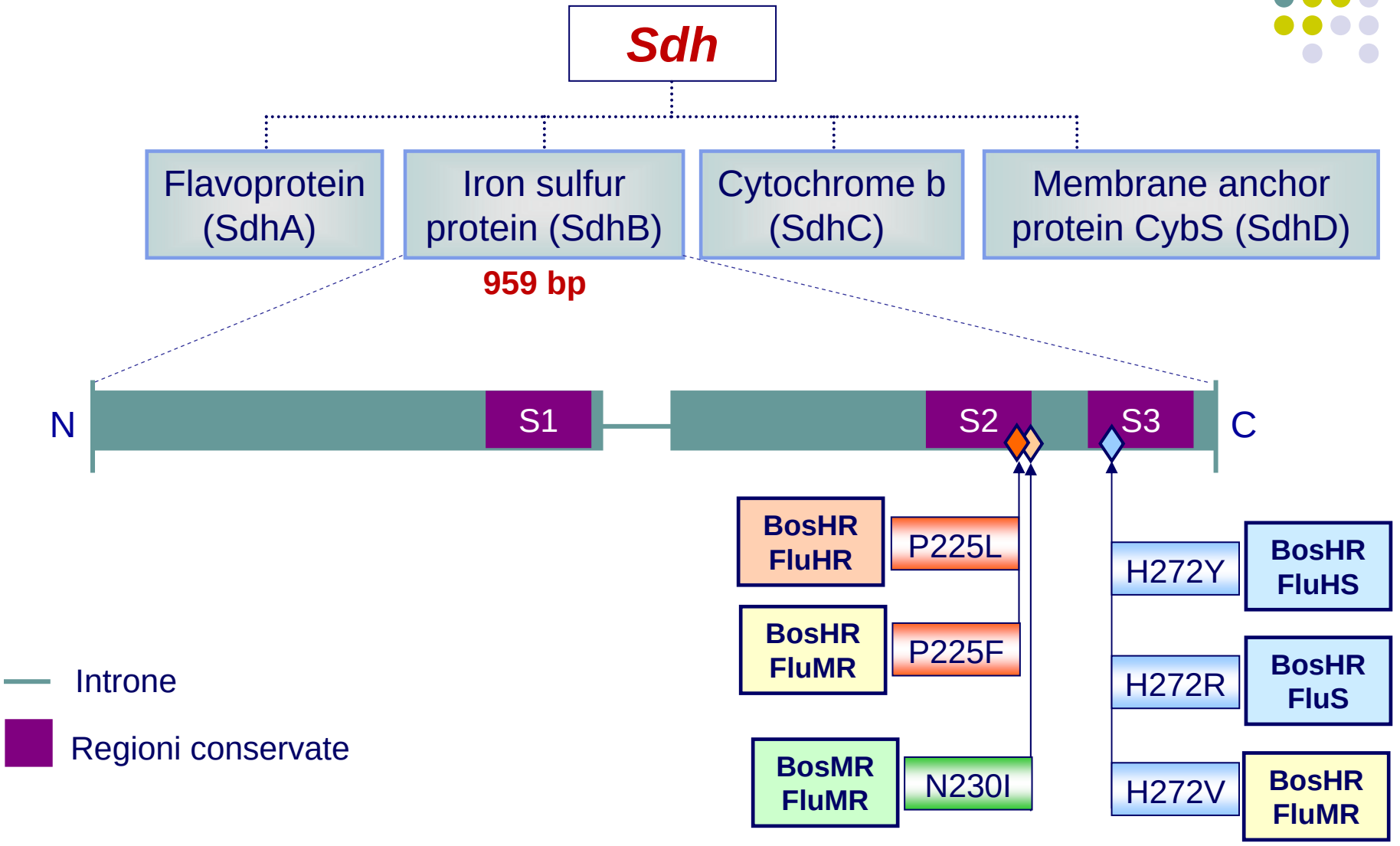
Daf1S

Normale sensibilità alla alta pressione osmotica

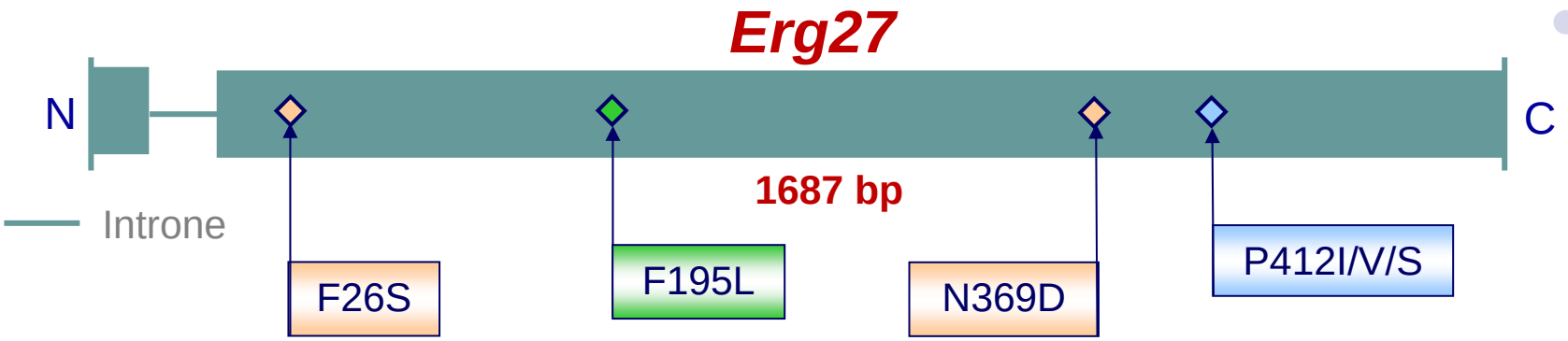
Ipersensibilità alla alta pressione osmotica

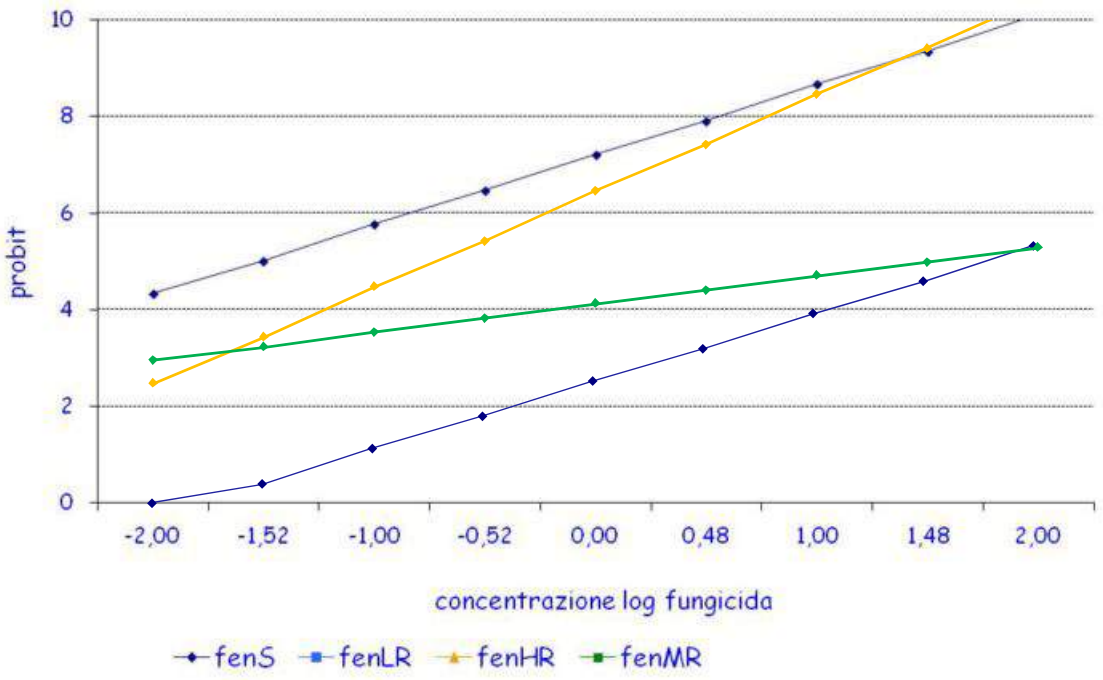
0 5 30 µg ml^{-1} vinclozolin

Fungicidi SDHI



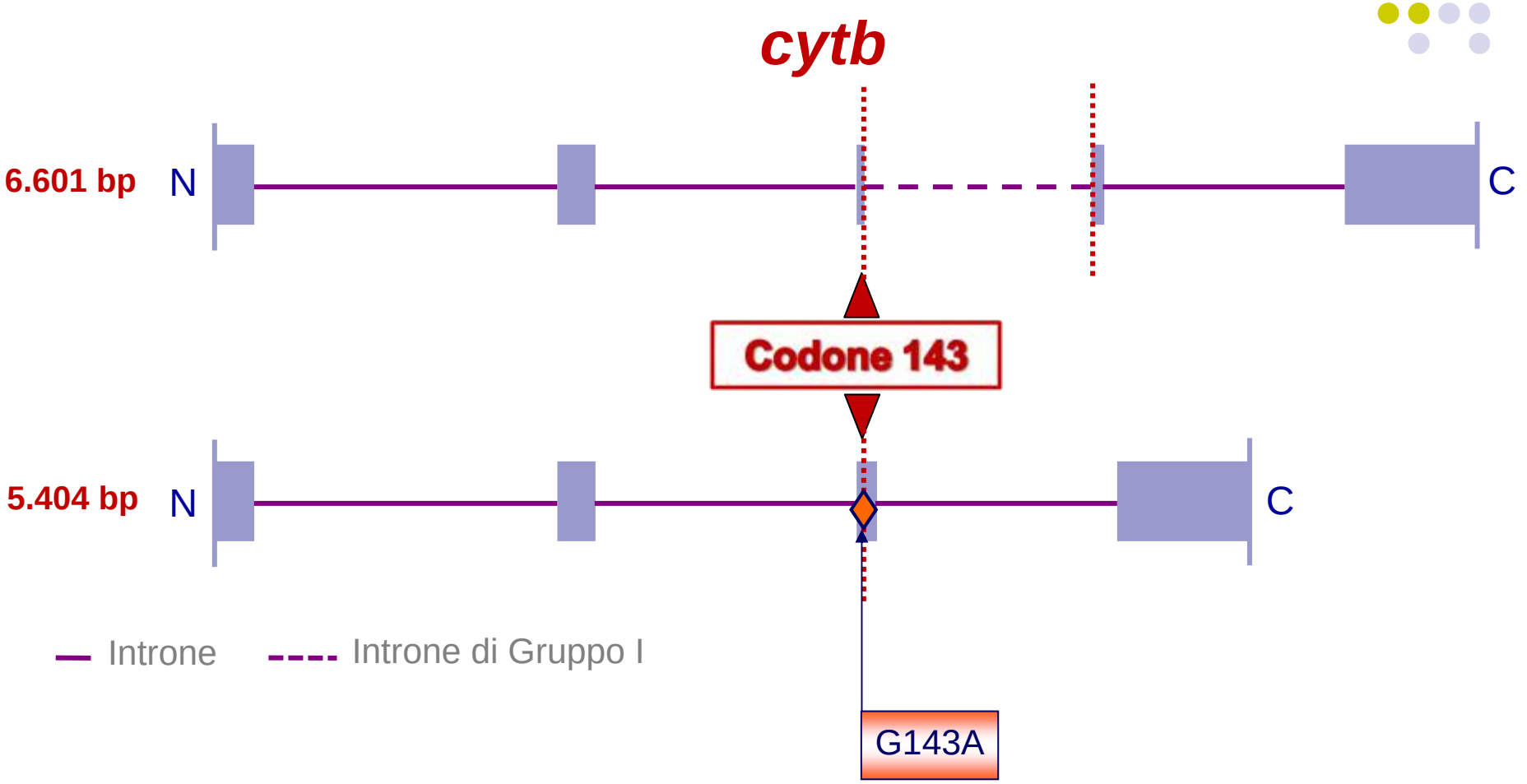
Fenhexamid





Fenotipo	CE_{50}	CMI
S	0,01-0,03	0,3
LR	0,03-0,1	1
MR	>100	>100
HR	>100	>100

Fungicidi QoI



Mutazioni nel gene della β-tubulina responsabili di resistenza in campo a benzimidazoli in funghi fitopatogeni

Codone	Sostituzione amminoacidica	Patogeno	Citazione bibliografica
6	His →Tyr	*Monilinia fructicola*	Ma *et al.*, 2003b
50	Tyr →Cys	*Cladobotryum dendroides*	McKay *et al.*, 1998
167	Phe → Tyr	*Cochliobolus heterostrophus* *Penicillium expansum*	Gafur *et al.*, 1998 Baraldi *et al.*, 2003
198	Glu → Ala	*Botryotinia fuckeliana* *Helminthosporium solani* *M. fructicola* *Penicillium aurantiogriseum* *Penicillium expansum* *Tapesia yallundae* *Tapesia acuformis* *Venturia inaequalis* *Venturia pirina*	Luck e Gillings, 1995 McKay e Cooke, 1997 Cunha e Rizzo, 2003 Ma *et al.*, 2003b Koenraadt *et al.*, 1992 Baraldi *et al.*, 2003 Koenraadt *et al.*, 1992 Albertini *et al.*,1999 Koenraadt *et al.*, 1992
	Glu → Gln	*T. acuformis* *T. yallundae* *H. Solani*	Albertini *et al.*, 1999 McKay e Cooke, 1997
	Glu → Gly	*T. acuformis* *T. yallundae* *V. Inaequalis*	Albertini *et al.*, 1999 Koenraadt *et al.*, 1992
	Glu → Lys	*M. fructicola* *P. aurantiogriseum* *P. digitatum* *Sclerotinia homoeocarpa* *V. inaequalis* *P. expansum* *T. yallundae* *T. acuformis*	Koenraadt *et al.*, 1992 Albertini *et al.*, 1999 Baraldi *et al.*, 2003 Albertini *et al.*, 1999
	Glu → Val	*P. expansum*	Albertini *et al.*, 1999
200	Phe → Tyr	*P. aurantiogriseum* *P. italicum* *V. inaequalis* *V. pirina* *T. yallundae*	Koenraadt *et al.*, 1992 Albertini *et al.*, 1999
240	Leu → Phe	*Monilinia laxa T. yallundae*	Ma *et al.*, 2005 Albertini *et al.*, 1999

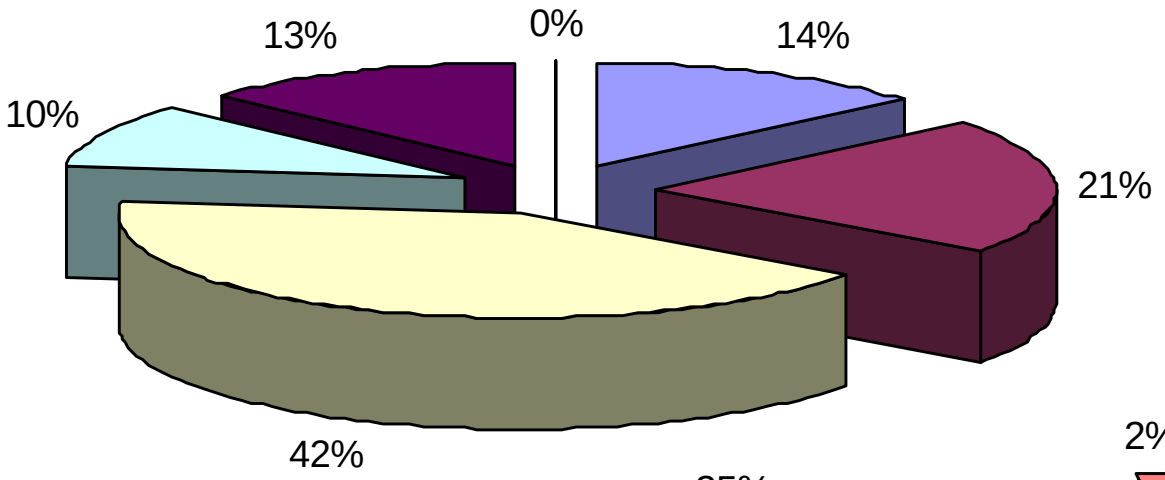
Mutazioni di resistenza a SDHI

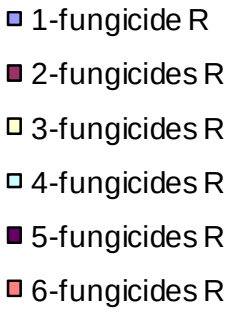
Succinato deidrogenasi		Organismo	Fenotipo di Resistenza[1]		Citazione bibliografica
Subunità	Sostituzione amminoacidica				
B	H257L	*Ustilago maydis*	CbxR	L	Keon *et al.*, 1991; Broomfield e Hargreaves, 1992
	H267Y/R/L, I269V	*Mycosphaerella graminicola*	CbxR	L	Skinner *et al.*, 1998
	H239L	*Pleurotus ostreatus*	CbxR	L	Honda *et al.*, 2000
	H228N	*Paracoccus denitrificans*	CbxR	L	Matsson e Hederstedt, 2001
	H229L	*Xanthomonas campestris*	CbxR	L	Li *et al.*, 2006
	H277Y/R	*Alternaria alternata*	BosR	C	Avenot *et al.*, 2008b
	H278Y	*Corynespora cassiicola*	BosR	C	Ishii *et al.*, 2008
	P225L/T/F; N230I; H272Y/R/L	*Botryotinia fuckeliana*	BosR	L e C	Stammler *et al.*, 2007; De Miccolis Angelini *et al.*, 2007; Leroux *et al.*, 2010
	H277R/Y	*Didymella bryoniae*	BosR	C	Stevenson *et al.*, 2008
	H ->Y	*Podosphaera xanthii*	BosR	C	BASF 2007 (FRAC)
	H249Y/L/N	*Aspergillus oryzae*	CbxR	L	Shima *et al.*, 2009
C	N80K	*Coprinus cinereus*	CbxR	L	Ito *et al.*, 2004
	H134R	*A. alternata*	BosR	C	Avenot *et al.*, 2009
	S73P	*C. cassiicola*	BosR	C	Glaettli *et al.*, 2009
	T90I	*A. oryzae*	CbxR	L	Shima *et al.*, 2009
D	D89G	*P. denitrificans*	CbxR	L	Matsson *et al.*, 1998
	D123E, 133R	*A. alternata*	BosR	C	Avenot *et al.*, 2009
	S89P	*C. cassiicola*	BosR	C	Glaettli *et al.*, 2009
	D132R	*Sclerotinia sclerotiorum*	BosR	C	Glaettli *et al.*, 2009
	D124E	*A. oryzae*	CbxR	L	Shima *et al.*, 2009
	H132R	*B. fuckeliana*	BosR	C	Leroux *et al.*, 2010

Resistenza multipla

Vite

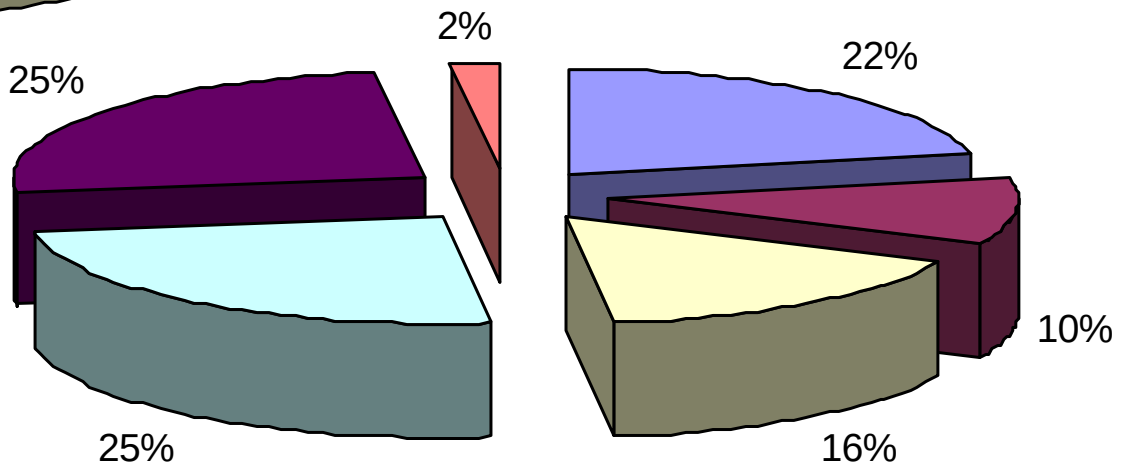
230 isolati





Fragola

431 isolati



Meccanismi di resistenza

- Decremento affinità del sito reattivo
- Decremento permeabilità membrane (MultiDrug resistance)
- Compensazione
- Circonvenzione
- Detossificazione
- Altri

Meccanismi di resistenza

Fungicide class	Mechanism of resistance
Benzimidazoles	Mutations in the β-tubulin gene
	Unknown mechanisms
Sterol demethylation inhibitors	Overexpression of the ATP-binding cassette transporters
	Mutations in the 14α-demethylase (cyp51) gene
	Overexpression of the cyp51 gene
Qo inhibitors	Mutations in the mitochondrial cytochrome b (cyt b) gene
	Alternative oxidase activation
Dicarboximide fungicides	Mutations in the two-component histidine kinase gene
	Mutations in the ubc1 gene (cAMP dependent protein kinase)
	Unknown mechanisms

MultiDrug Resistance

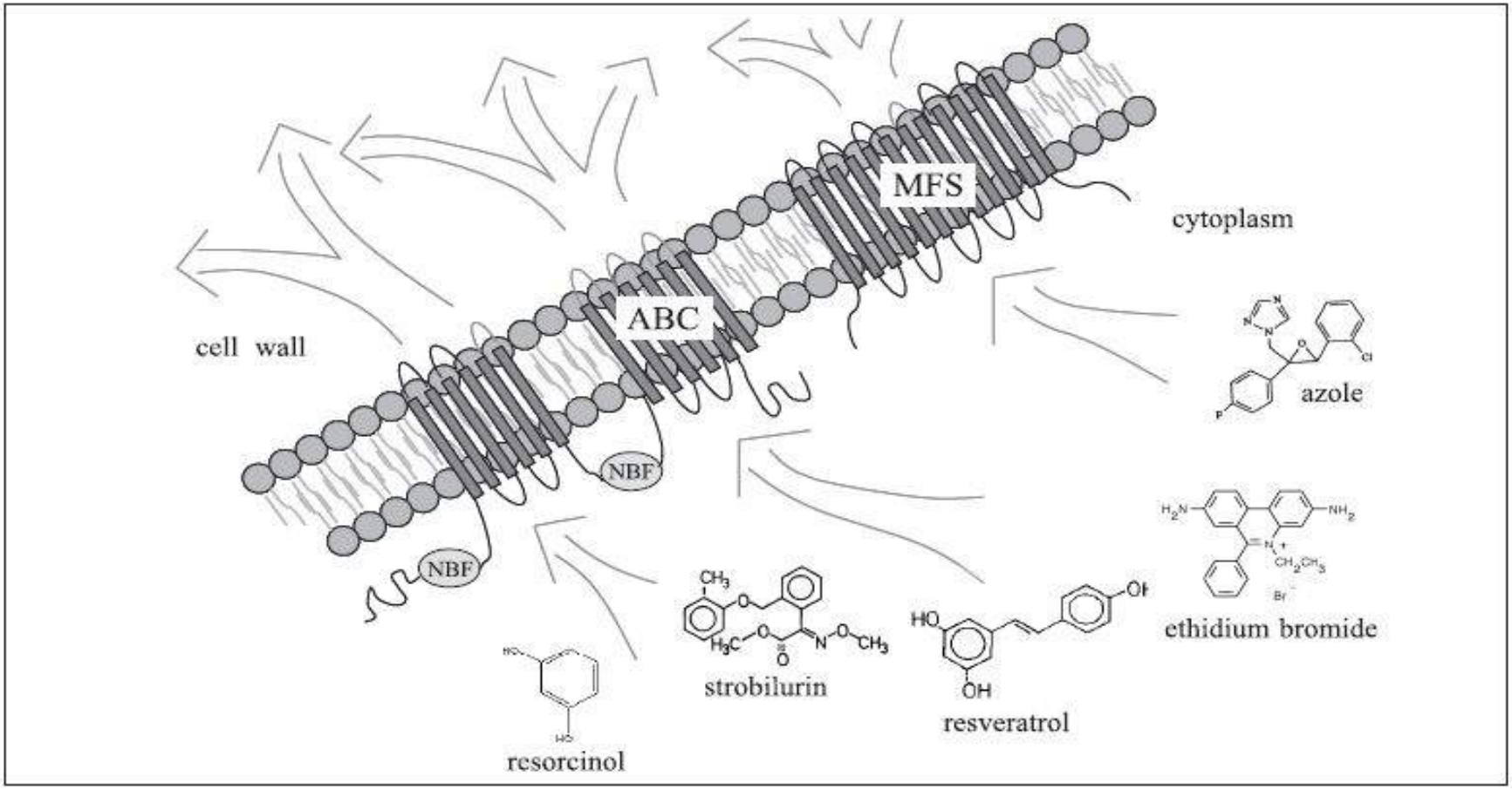
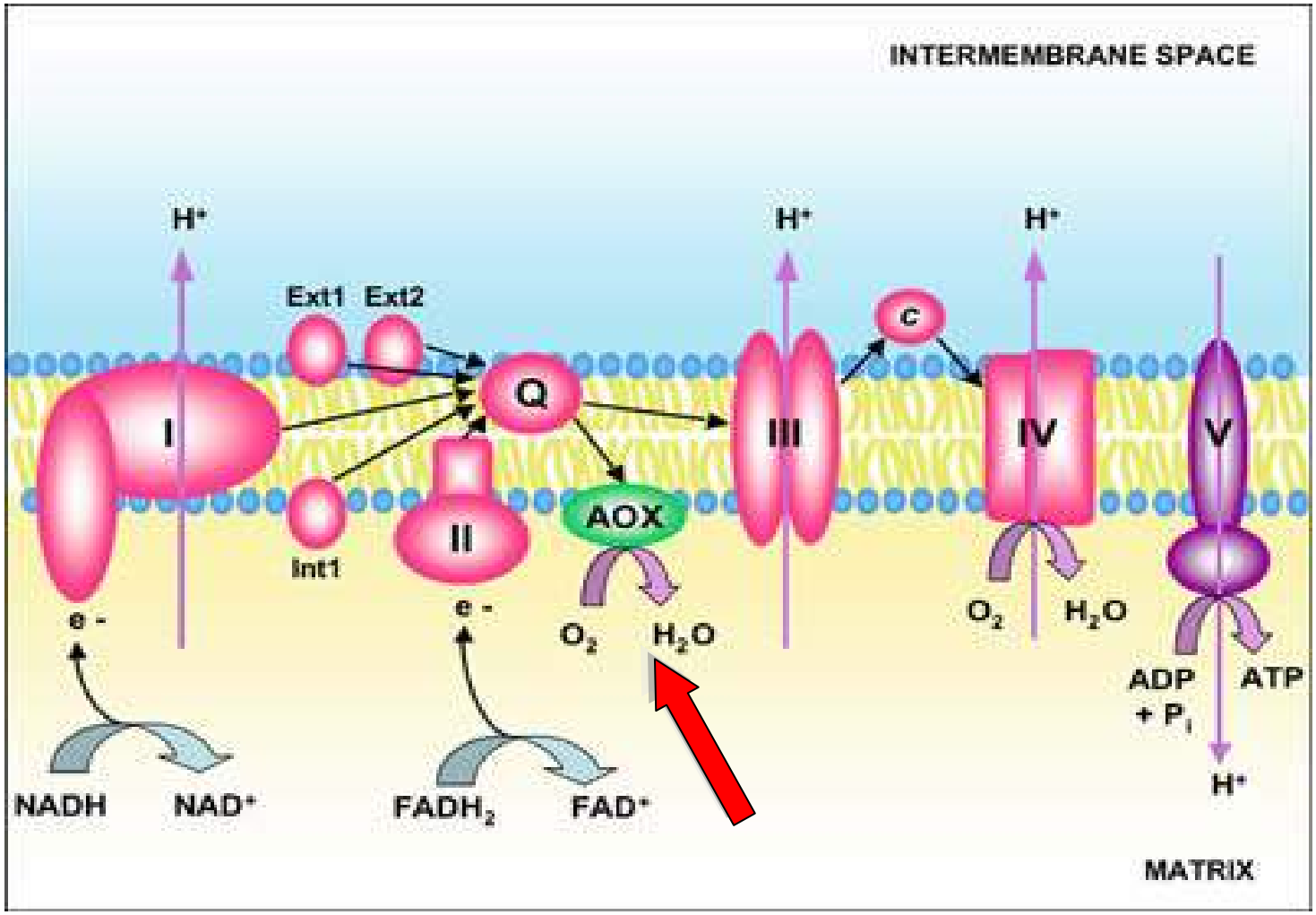


Figure 3: Diagram of a fungal ABC- and an MFS-transporter. The ABC transporter consists of two repeats of a nucleotide binding domain (NBF) and six trans-membrane domains; the MSF transporter has 12 trans-membrane domains. The membrane efflux pumps can transport structurally diverse molecules such as strobilurin and azole fungicides, the fluorescent dye ethidium bromide, and the plant defense compounds resveratrol and resorcinol. After Del Sorbo *et al*. (13), modified.

Circonvenzione



Fungicidi: rischio intrinseco

Fattori
Meccanismo d’azione
Determinismo genetico
Meccanismo di resistenza
Fitness dei ceppi resistenti
Casi pregressi di resistenza
Resistenza incrociata

Fungicidi: rischio intrinseco

ALTO	MODERATO	BASSO
Benzimidazoli	Aminopirimidine	Rame
Dicarbossimidi	Triazoli	Zolfo
Fenilammidi	Cymoxanil	Ditiocarbammati
Anilinopirimidine	CAA	Chlorothalonil
QoI – QiI - QxI	Fenilpirroli	Ftalimmidi
SDHI	Fenexamid	Quinoxyfen

Patogeni: rischio intrinseco

Fattore	Peso
N. di generazioni	X 4
Dispersione spore	X 3
Produzione spore	X 2
Storia resistenza	X 2
Frequenza di manifestazione e protezione	X 3
Totale	**(Σ)**

Punteggio	Classe di rischio
14-34	I = basso
35-59	II = medio
>60	III = alto

Rischio per patogeno/coltura

Elevato	Medio	Basso
Botrytis cinerea – vite e varie	*Bremia lactucae* – lattuga	*Alternaria* spp. – varie
Blumeria graminis – grano	*Cercospora* spp. – varie	*Colletotrichum* spp. – varie
Penicillium spp. – agrumi	*Monilinia* spp. - varie	*Fusarium* spp.- varie
Phytophthora infestans (PA) – patata, pomodoro	*Phytophthora infestans* (no PA) – patata, pomodoro	*Phytophthora* spp. (soil borne) – varie
Plasmopara viticola – vite	*Sclerotinia spp. - varie*	*Puccinia* spp. - varie
Pseudoperonospora cubensis - cucurbitacee	*Mycosphaerella graminicola* - grano	*Rhizoctonia* spp. – varie
Sphaerotheca fuliginea - cucurbitacee	*Erysiphe necator* - vite	*Tilletia* spp. – cereali
Venturia spp. - pomacee	*Peronospora* spp. - varie	*Ustilago* spp. - cereali

Rischio agronomico

- Gestione intensiva della coltura
- Modalità della protezione della coltura
- Numerosi trattamenti con fungicidi “a rischio” aventi lo stesso meccanismo d’azione
- Ambiente confinato (serre)

Rischio combinato

Benzimidazoli Dicarbossimidi Fenilammidi e QoI	3	3	6	9
Carbossianilidi IBS Fenilpirroli	2	2	4	6
Rame Ditiocarbammati Ftalimmidi Zolfo Induttori SAR	1	1	2	3
Rischio del fungicida ↑		1	2	3
Rischio della malattia →		Trasmessi da seme (es. *Ustilago*) Trasmessi dal terreno (*Phytophthora*) Ruggini dei cereali	*Rhyncosporium* *Septoria*	Ticchiolatura, Oidio cereali, *Botrytis cinerea*, *Phytophthora infestans*, *Penicillium* su agrumi ecc.

Rischio combinato benzimidazoli

Botryotinia fuckeliana vs. Monilia laxa

Prevenzione e gestione

Riduzione della pressione di selezione sulle popolazioni fungine operata dai trattamenti mediante modificatori del rischio:

- **Strategie di protezione integrata**
- Limitazioni all'impiego
- Adozione di miscele fra fungicidi con diverso meccanismo d'azione

Necessità di aperta collaborazione fra tutte le parti interessate?????

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Welcome

Welcome To FRAC

Fungicides have become an integral part of efficient food production. The loss of a fungicide to agriculture through resistance is a problem that affects us all.

FRAC works to prolong the effectiveness of fungicides liable to encounter resistance problems and to limit crop losses should resistance appear.

Site
- Disclaimer
- Impressum

What's New

2006-01-27 - First report of the new CAA Fungicides Working Group is now online

The first report for the CAA Working Group has been published on the FRAC Website. Monitoring information for 2005 as well as the CAA fungicide use guidelines for 2006 are presented.

2006-01-24 - AP Working Group update now available

The 2005 summary for the AP Working Group has been updated. Monitoring information for 2005 as well as the AP fungicide use guidelines for 2006 are included.

www.frac.info

Internet