

The logo for SCYNEXIS, featuring the word in a bold, white, sans-serif font. The letter 'X' is stylized with a small circle above it, resembling a molecular structure or a specific chemical element. The background is a gradient of orange and purple with a faint, large-scale pattern of circular structures, possibly representing a biological or chemical process.

SCYNEXIS

# Difficoltà nello Sviluppo di Farmaci Antifungini Sistemici

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# Antibatterici e Antifungini

1930

Antibacterials

2016

sulfacetamide spiramycin cloxacillin doxycycline cefmetazole azithromycin daptomycin  
 sulfamerazine vancomycin clindamycin cefadroxil netilmicin ofloxacin levofloxacin  
 oxytetracycline lymecycline azlocillin cefoperazone cefodizime ceftazidime  
 virginiamycin rifampicin fosfomicin cefaclor cefixime cefoperazone/sulbactam doripenem  
 benzathine penicillin gentamicin amoxicillin cefotaxime sultamicillin dirithromycin quinupristin/dalfopristin telavancin  
 thiamphenicol ampicillin nalidixic acid cefamandole ciprofloxacin meropenem  
 sulfamethizole chloramphenicol sulfamethoxazole minocycline ceftriaxone ampicillin/sulbactam telithromycin ceftolozane/tazobactam  
 methicillin  
 sulfadiazine cefalotin tinidazole cefotiam isepamicin ceftibuten  
 benzylpenicillin bacampicillin cefsulodin mupirocin piperacillin/tazobactam bedaquiline  
 trimethoprim carbenicillin talampicillin co-amoxiclav aztreonam midecamycin ceftaroline  
 penicillin G procaine cefalexin amikacin mezlocillin norfloxacin rifapentine clarithromycin tigecycline  
 tetracycline  
 neomycin spectinomycin tobramycin cefonicid cefprozil  
 gramicidin S erythromycin fusafungine cefsulodin imipenem/cilastatin roxithromycin ceftazidime/avibactam  
 phenoxymethylpenicillin arbekacin cefotetan cefpodoxime moxifloxacin linezolid dalbavancin  
 chlortetracycline fusidic acid pivampicillin ceftazidime lomefloxacin rifloxacin fidaxomicin  
 streptomycin metronidazole cefazolin ceftazidime cefpiramide sparfloxacin tedizolid  
 colistin cefradine cefuroxime cefmenox rifaximin panipenem/betamipron

1930

Antifungals

2016

Amphotericin B Itraconazole Anidulafungin  
 Ketoconazole Caspofungin Isavuconazole  
 Fluconazole Posaconazole  
 Voriconazole  
 Micafungin

# Scarsità di Antifungini Sistemici

- Only Three Classes and Nine Products
  - **Polyens**: amphotericin B
  - **Azoles**: itraconazole, fluconazole, voriconazole, posaconazole, isavuconazole
  - **Echinocandins**: caspofungin, micafungin, anidulafungin
- Systemic fungal infections are increasing
  - Conditions or Treatments affecting the immuno-system
  - Increased incidence of antifungal resistance
  - Mortalità remains very high

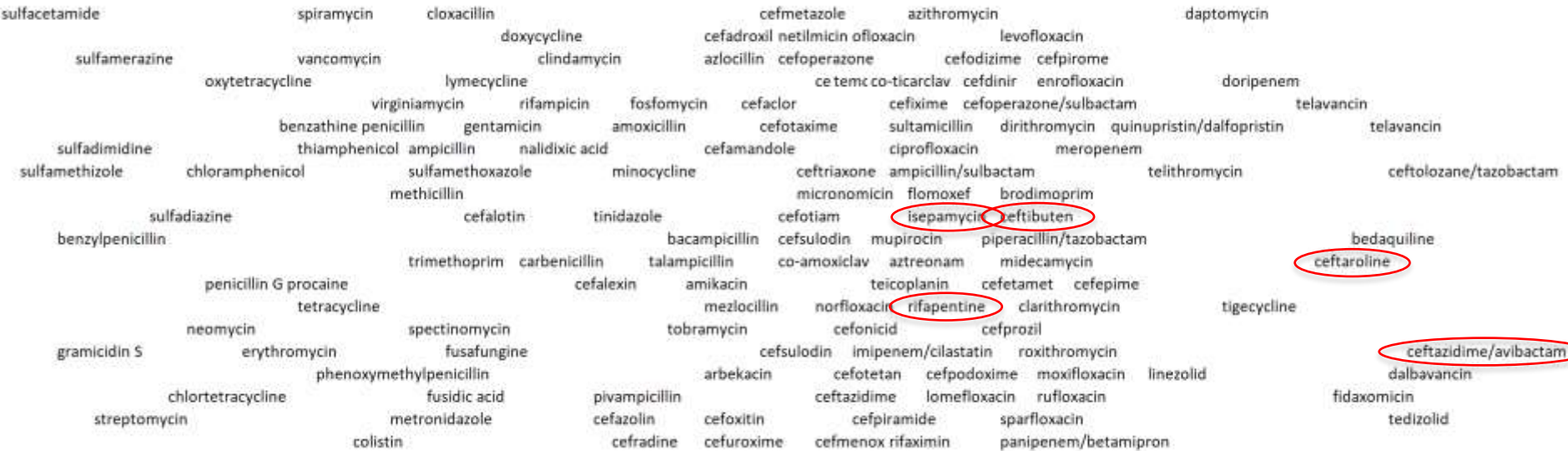
# Antibatterici e Antifungini...

## La mia esperienza...

1930

Antibacterials

2016



1930

Antifungals

2016



# Antifungino Sistemico Ideale

- Mechanism of action with no or minimal off-target effects
- Ideally, fungicidal activity
  - Immunosuppressed patients have little ability to clear infection
- Spectrum of action
  - Broad to include new species
  - If narrow, diagnostic tools are needed
- Safety and tolerability are critical in these fragile patient
- Avoid Drug-Drug Interactions (DDI)

# I Problemi con gli Antifungini Sistemici

- Why is so difficult to develop novel systemic antifungals?
  - Biology
  - Clinical Development and Regulatory
  - Inadequate Public Support
  - The Crisis of Anti-Infectives Biotechnology



# Biologia: Efficacia e Tossicità

- Unique biological targets for fungi are rare
  - Very similar metabolism pathways in all eukaryotic cells, being fungal or human
- Targets for currently available antifungals
  - Cell membrane (ergosterol) for polyens e azoles
  - Cell wall (glucan synthase) for echinocandins
- Toxicity
  - Significant off-target effect of polyenes and azoles
- Screening methods challenges
  - Limitations of the classic growth inhibition assays
  - New assays assessing metabolic activity
- Activity against rare and difficult-to-treat molds

# Sviluppo Clinico e Requisiti Normativi

- **General issues with enrollment**
  - Invasive fungal infections are not that common
  - Patients have significant comorbidities
  - Diagnosis of fungal infections is complex and takes time
- **Issues with the “classic” randomized design**
  - Ethical issues in performing dose finding studies
  - Selection bias to enroll “healthier” patients
  - Non-inferiority design do not provide adequate differentiation
  - Lack of regulatory accepted rapid diagnostic tools as endpoints
- **Issues with “open-label” uncontrolled design**
  - Difficult to interpret but it may work in limited instances
- **Long enrollment time and high costs**



# Supporto Pubblico Limitato

- Some general support for anti-infectives
  - GAIN Act in the U.S. in 2012 with QIDP Status
- ... but inadequate support for antifungals
  - Little understanding of fungal infections among legislators
  - Little/No support for antifungals (e.g. BARDA grants)
- Clinical development for antifungals
  - Long timelines (5 to 10 years)
  - High Costs (300 to 500 million dollars)

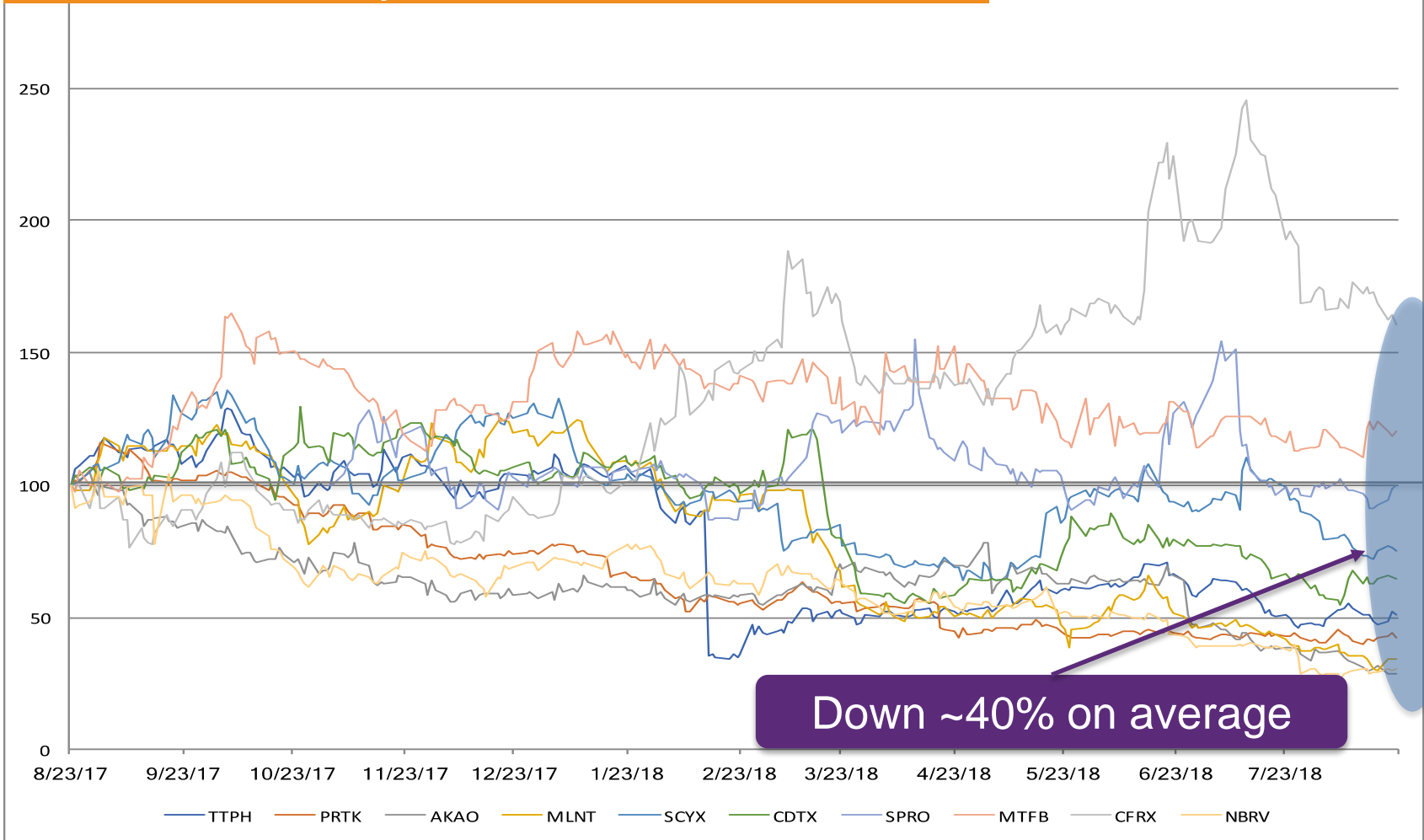
GAIN: Generating Antibiotic Incentives Now

QIDP: Qualified Infectious Disease Product

BARDA: Biomedical Advanced Research and Development Authority

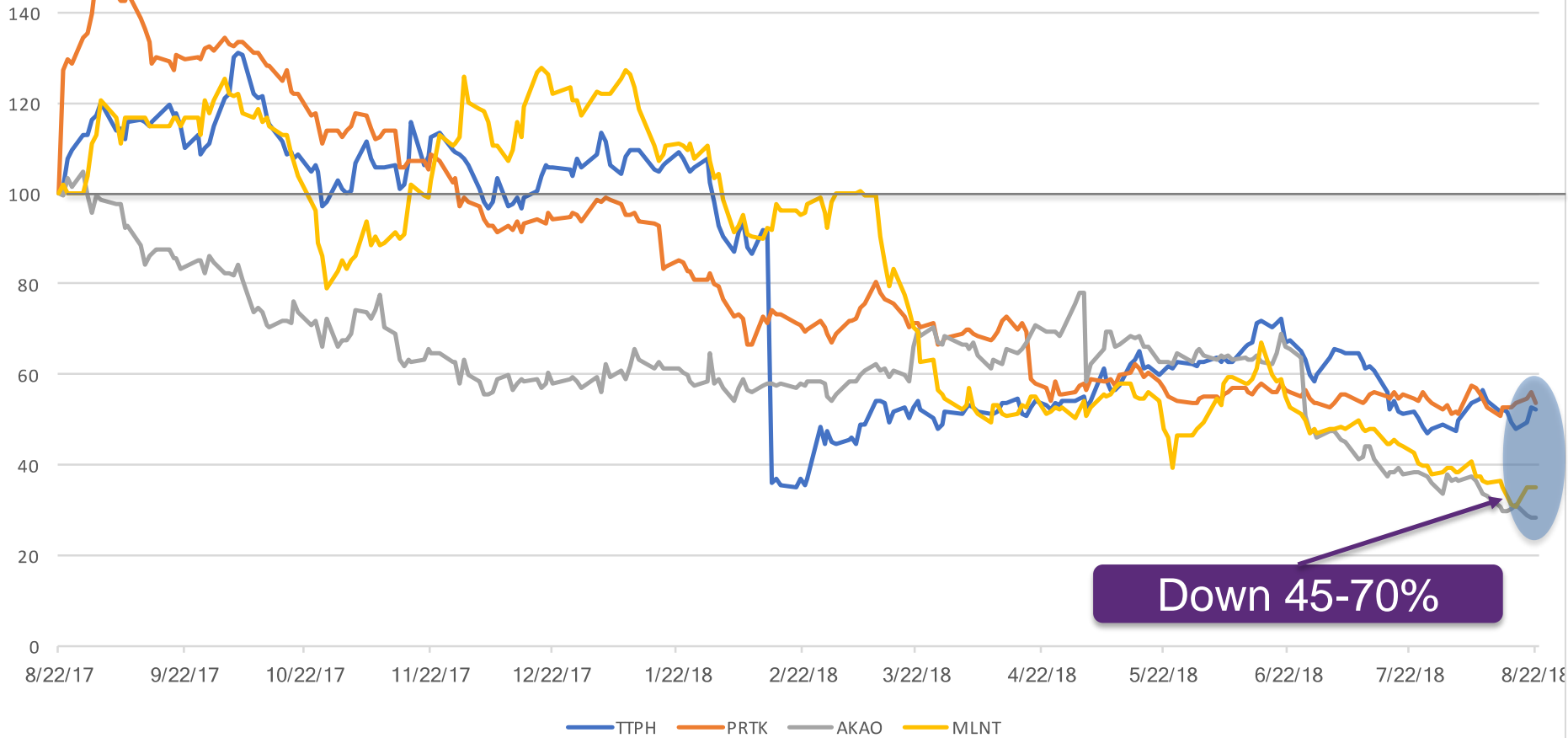
# Crisi del Biotech in Anti-Infettivi

## A-I Indexed 1-year Performance



# Compagnie Biotech in A-I Pronte al Lancio

## Indexed 1-year Performance



# C'e' Speranza?

- Many scientists and biotech companies remain committed to anti-infectives
  - Understanding the need of new antibiotics
  - Accepting the cyclic nature of anti-infectives business
- Promoting new regulations to foster the development of new anti-infective products
- ... and for antifungals?
  - New classes of antifungals under development

# Nuovi Antifungini in Sviluppo

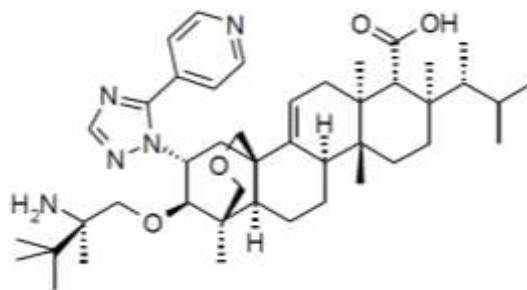
- **Cidara Rezafungin**
  - Analog of anidulafungin with longer half life allowing once-a-week dosing
- **Amplify APX001**
  - Glycosyl phosphatidylinositol (GPI) inhibitor
  - Broad spectrum activity against *Candida*, *Aspergillus* and other molds
- **Vical ASP2397**
  - Siderophore iron transporter 1 (Sit1)
  - Active especially on *Aspergillus* and other molds
- **F2G F901318**
  - Dihydrorotate dehydrogenase inhibitor
  - Active on *Aspergillus* and *Scedosporium*
- **SCYNEXIS Ibrexafungerp (SCY-078)**
  - Novel class of glucan synthase inhibitors
  - Active against *Candida*, *Aspergillus* and *Pneumocysts*

# Ibrexafungerp (SCY-078): Novel Triterpenoid Antifungal

**Broad Spectrum**  
*Candida*, *Aspergillus* and  
*Pneumocystis*  
2000+ strains tested

**Activity vs. Resistant  
Strains**  
Including MDR strains

**Oral Formulation**  
**Entering Phase 3**  
IV in pre-clinical development



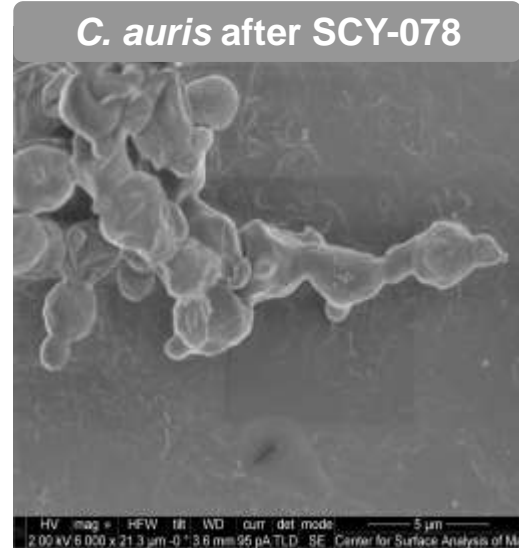
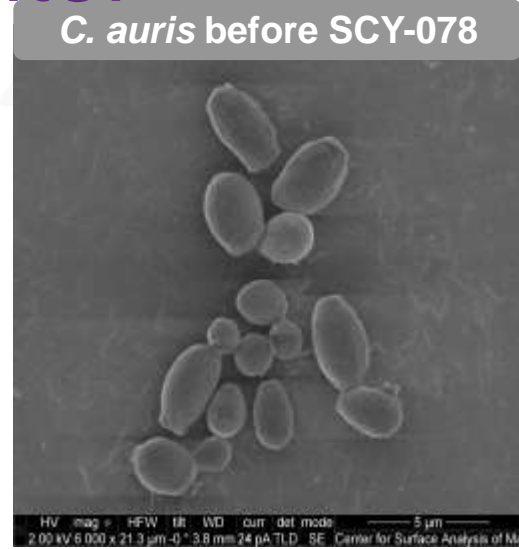
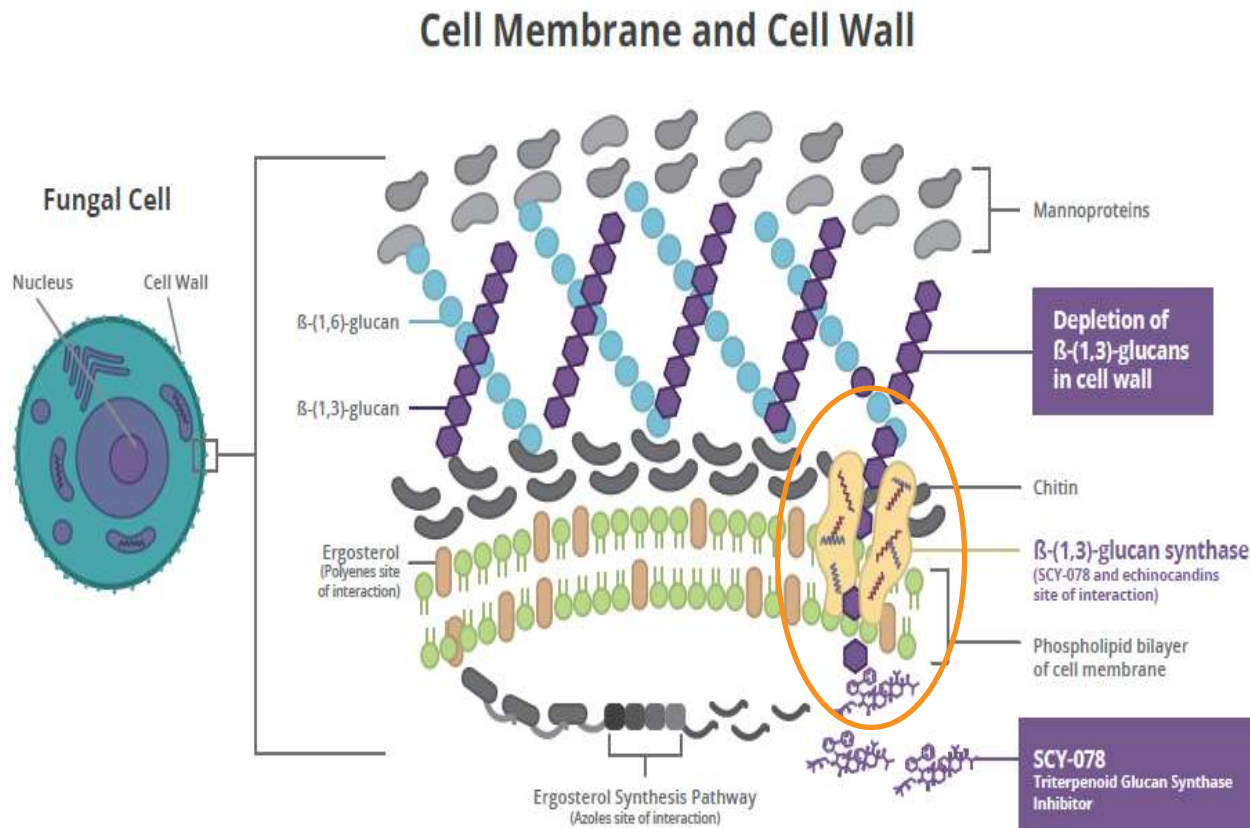
**Fungicidal vs. *Candida***  
Benefits over fungistatic  
agents

**Safe and Well-Tolerated**  
450+ subjects exposed

**20-hour Half-Life**  
**High Tissue Penetration**  
**Low Risk of DDIs**

**Worldwide Rights and Long Exclusivity (IP up to 2035)**  
**QIDP + Fast Track designations for Invasive Candidiasis, Aspergillosis and VVC**

# Ibrexafungerp (SCY-078): A New Glucan Synthase Inhibitor



**Validated MoA**  
Minimal risk of off-target effects  
Differentiated binding vs. echinocandins



# Conclusioni

- Le infezioni fungine e la resistenza agli antifungini è un problema di salute pubblica sempre maggiore
- Mancanza di alternative per il trattamento sistemico di infezioni fungine
- Identificare, sviluppare e finanziare nuovi antifungini, efficaci e sicuri, è sempre più difficile
- Però ci sono ancora compagnie e ricercatori che rimangono dedicati agli anti-infettivi, con anche alcuni nuovi e promettenti antifungini



# Grazie!

A word cloud featuring the phrase 'Thank you' in numerous languages and scripts. The largest text is 'thank you' in a bold, red, sans-serif font. Surrounding it are other translations in various sizes and colors, including: 'danke' (blue), 'gracias' (green), 'merci' (orange), 'dziękuję' (pink), 'arigatō' (purple), 'terima kasih' (yellow), 'sukriya' (dark blue), 'agat' (brown), 'mochchakkeram' (blue), 'ngiyabonga' (red), 'teşekkür ederim' (purple), 'chokwane murakoze' (yellow), 'obrigado' (green), 'sagolun' (blue), 'dank je' (green), 'misaotra matondo' (blue), 'paldies grazzi' (yellow), 'tapadh leat' (orange), 'hvala' (yellow), 'mauruuru' (blue), 'koşonöm' (blue), 'mami nandri' (red), 'kiitos dankie' (green), 'danyavad' (green), 'nani' (red), 'nami' (red), 'bayanatataa' (green), 'gracie' (green), 'sobodid' (green), 'dekuji' (green), 'mesim' (green), 'didid madloba' (green), 'kam sah hamnida' (green), 'rahmat' (green), 'najjis tuke' (green), 'dior' (green), 'chhorakaloutioun' (green), 'gratias ago' (green), 'gracies' (green), 'sulpáy' (green), 'raibh' (purple), 'maith' (purple), 'mamnun' (purple), 'djiere dieut' (purple), 'lau' (purple), 'djia' (purple), 'dialch' (purple), 'dhanyavadagalu' (purple), 'shukriya' (purple), 'mercim' (purple), 'merci' (orange), 'xixie' (orange), 'euχαριστώ' (orange), 'tanemirt rahmet' (orange), 'arigatō' (purple), 'takk' (purple), 'dakujem' (purple), 'trugarez' (purple), 'merci' (purple), 'misaotra' (blue), 'matondo' (blue), 'paldies' (yellow), 'grazzi' (yellow), 'mahalo' (red), 'tapadh leat' (orange), 'hvala' (yellow), 'asante manana' (red), 'obrigada' (red), 'murakoze' (yellow), 'chokwane' (yellow), 'tenki' (red), 'dankie' (green), 'danyavad' (green), 'mauruuru' (blue), 'koşonöm' (blue), 'mami nandri' (red), 'kiitos' (green), 'nani' (red), 'nami' (red), 'bayanatataa' (green), 'gracie' (green), 'sobodid' (green), 'dekuji' (green), 'mesim' (green), 'didid madloba' (green), 'kam sah hamnida' (green), 'rahmat' (green), 'najjis tuke' (green), 'dior' (green), 'chhorakaloutioun' (green), 'gratias ago' (green), 'gracies' (green), 'sulpáy' (green), 'raibh' (purple), 'maith' (purple), 'mamnun' (purple), 'djiere dieut' (purple), 'lau' (purple), 'djia' (purple), 'dialch' (purple), 'dhanyavadagalu' (purple), 'shukriya' (purple), 'mercim' (purple), 'merci' (purple), 'xixie' (orange), 'euχαριστώ' (orange), 'tanemirt rahmet' (orange), 'arigatō' (purple), 'takk' (purple), 'dakujem' (purple), 'trugarez' (purple), 'misaotra' (blue), 'matondo' (blue), 'paldies' (yellow), 'grazzi' (yellow), 'mahalo' (red), 'tapadh leat' (orange), 'hvala' (yellow), 'asante manana' (red), 'obrigada' (red), 'murakoze' (yellow), 'chokwane' (yellow), 'tenki' (red), 'dankie' (green), 'danyavad' (green), 'mauruuru' (blue), 'koşonöm' (blue), 'mami nandri' (red), 'kiitos' (green), 'nani' (red), 'nami' (red), 'bayanatataa' (green), 'gracie' (green), 'sobodid' (green), 'dekuji' (green), 'mesim' (green), 'didid madloba' (green), 'kam sah hamnida' (green), 'rahmat' (green), 'najjis tuke' (green), 'dior' (green), 'chhorakaloutioun' (green), 'gratias ago' (green), 'gracies' (green), 'sulpáy' (green), 'raibh' (purple), 'maith' (purple), 'mamnun' (purple), 'djiere dieut' (purple), 'lau' (purple), 'djia' (purple), 'dialch' (purple), 'dhanyavadagalu' (purple), 'shukriya' (purple), 'mercim' (purple), 'merci' (purple), 'xixie' (orange), 'euχαριστώ' (orange), 'tanemirt rahmet' (orange), 'arigatō' (purple), 'takk' (purple), 'dakujem' (purple), 'trugarez' (purple). Other visible words include 'Баярлалаа' (blue), 'спасибо' (red), 'vinaka' (green), 'blagodaram' (green), 'kia ora' (green), 'barka' (green), 'welalim' (green), 'tack' (green), 'ngiyabonga' (red), 'teşekkür ederim' (purple), 'spas' (green), 'dank je' (green), 'misaotra' (blue), 'matondo' (blue), 'paldies' (yellow), 'grazzi' (yellow), 'mahalo' (red), 'tapadh leat' (orange), 'hvala' (yellow), 'mauruuru' (blue), 'koşonöm' (blue), 'mami nandri' (red), 'kiitos dankie' (green), 'danyavad' (green), 'mauruuru' (blue), 'koşonöm' (blue), 'mami nandri' (red), 'kiitos' (green), 'nani' (red), 'nami' (red), 'bayanatataa' (green), 'gracie' (green), 'sobodid' (green), 'dekuji' (green), 'mesim' (green), 'didid madloba' (green), 'kam sah hamnida' (green), 'rahmat' (green), 'najjis tuke' (green), 'dior' (green), 'chhorakaloutioun' (green), 'gratias ago' (green), 'gracies' (green), 'sulpáy' (green), 'raibh' (purple), 'maith' (purple), 'mamnun' (purple), 'djiere dieut' (purple), 'lau' (purple), 'djia' (purple), 'dialch' (purple), 'dhanyavadagalu' (purple), 'shukriya' (purple), 'mercim' (purple), 'merci' (purple), 'xixie' (orange), 'euχαριστώ' (orange), 'tanemirt rahmet' (orange), 'arigatō' (purple), 'takk' (purple), 'dakujem' (purple), 'trugarez' (purple), 'misaotra' (blue), 'matondo' (blue), 'paldies' (yellow), 'grazzi' (yellow), 'mahalo' (red), 'tapadh leat' (orange), 'hvala' (yellow), 'asante manana' (red), 'obrigada' (red), 'murakoze' (yellow), 'chokwane' (yellow), 'tenki' (red), 'dankie' (green), 'danyavad' (green), 'mauruuru' (blue), 'koşonöm' (blue), 'mami nandri' (red), 'kiitos' (green), 'nani' (red), 'nami' (red), 'bayanatataa' (green), 'gracie' (green), 'sobodid' (green), 'dekuji' (green), 'mesim' (green), 'didid madloba' (green), 'kam sah hamnida' (green), 'rahmat' (green), 'najjis tuke' (green), 'dior' (green), 'chhorakaloutioun' (green), 'gratias ago' (green), 'gracies' (green), 'sulpáy' (green), 'raibh' (purple), 'maith' (purple), 'mamnun' (purple), 'djiere dieut' (purple), 'lau' (purple), 'djia' (purple), 'dialch' (purple), 'dhanyavadagalu' (purple), 'shukriya' (purple), 'mercim' (purple), 'merci' (purple), 'xixie' (orange), 'euχαριστώ' (orange), 'tanemirt rahmet' (orange), 'arigatō' (purple), 'takk' (purple), 'dakujem' (purple), 'trugarez' (purple).