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NEW ZEALAND

New combination therapy for fungal infections

Drug development for “Super-Azoles”: New resistance inhibitor + azole

Dr Alex Tickle
Commercialisation Manager

What's it worth? Value and Opportunity

- Fungal infections: often difficult to treat and sometimes fatal
- Invasive fungal infections:
  - Rare but high level of mortality: early treatment and/or prophylaxis important
  - Candida and Aspergillus most common pathogens
- US$ 4.179 billion (2007)
  - Highly genericized, few new product launches
  - Toxicity concerns relating to major marketed drugs
- Three classes: Polyenes, Azoles and Echinocandins
- Growing unmet need for new antifungals due to increased incidence of resistant fungal infections

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Antifungal Market – US$ 4.179 Billion

- Most common antifungals: Amphotericin B and Fluconazole
- Biggest sales 2007:

– Lamisil (terbinafine)	$668m	(-16.6%; patent expired)	Novartis
– Vfend (voriconazole)	$599m	(+10.7%; exp. 2016)	Pfizer
– Cancidas (caspofungin)	$495m	(+4.0%; exp. 2013)	Merck
– Diflucan (fluconazole)	$377m	(-13.3%; expired)	Pfizer (J&J)
– Ambisome (amphotericin B)	$310m	(-2.3%; NA)	Gilead/Astellas
– Sporanox (itraconazole)	$295m	(-10.7%; exp. 2014)	J&J
– Noxafil (posaconazole)	$ 85m	(+17.5%; exp. 2014)	SP/Merck
– Abelcet (lipo-amphotericin B)	$ 54m	(-13.9%; NA)	Enzon/στ

- Most recent: echinocandins (caspofungin- Merck, micafungin- Astellas, anidulafungin- Pfizer)

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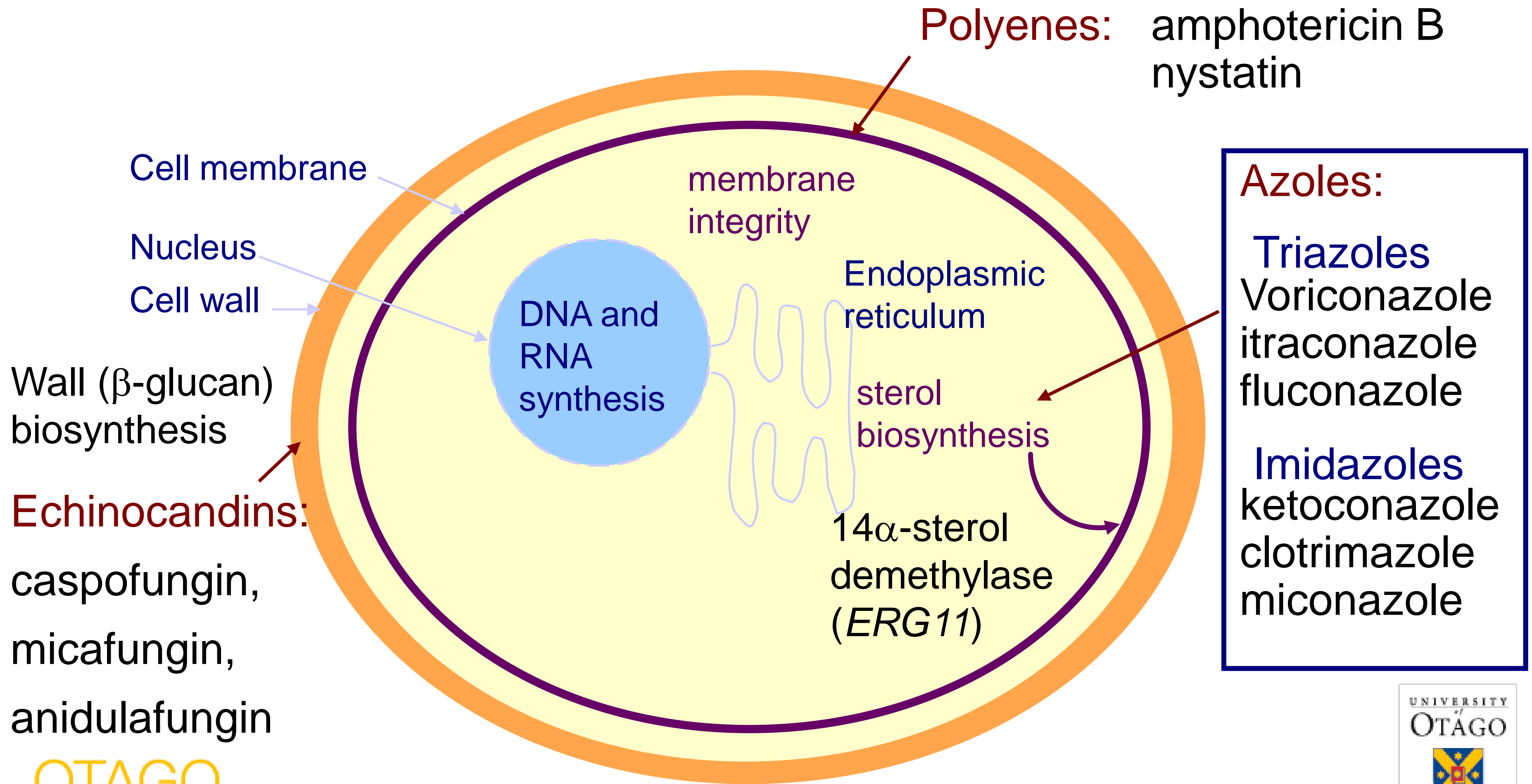
Antifungal drugs: sites of action



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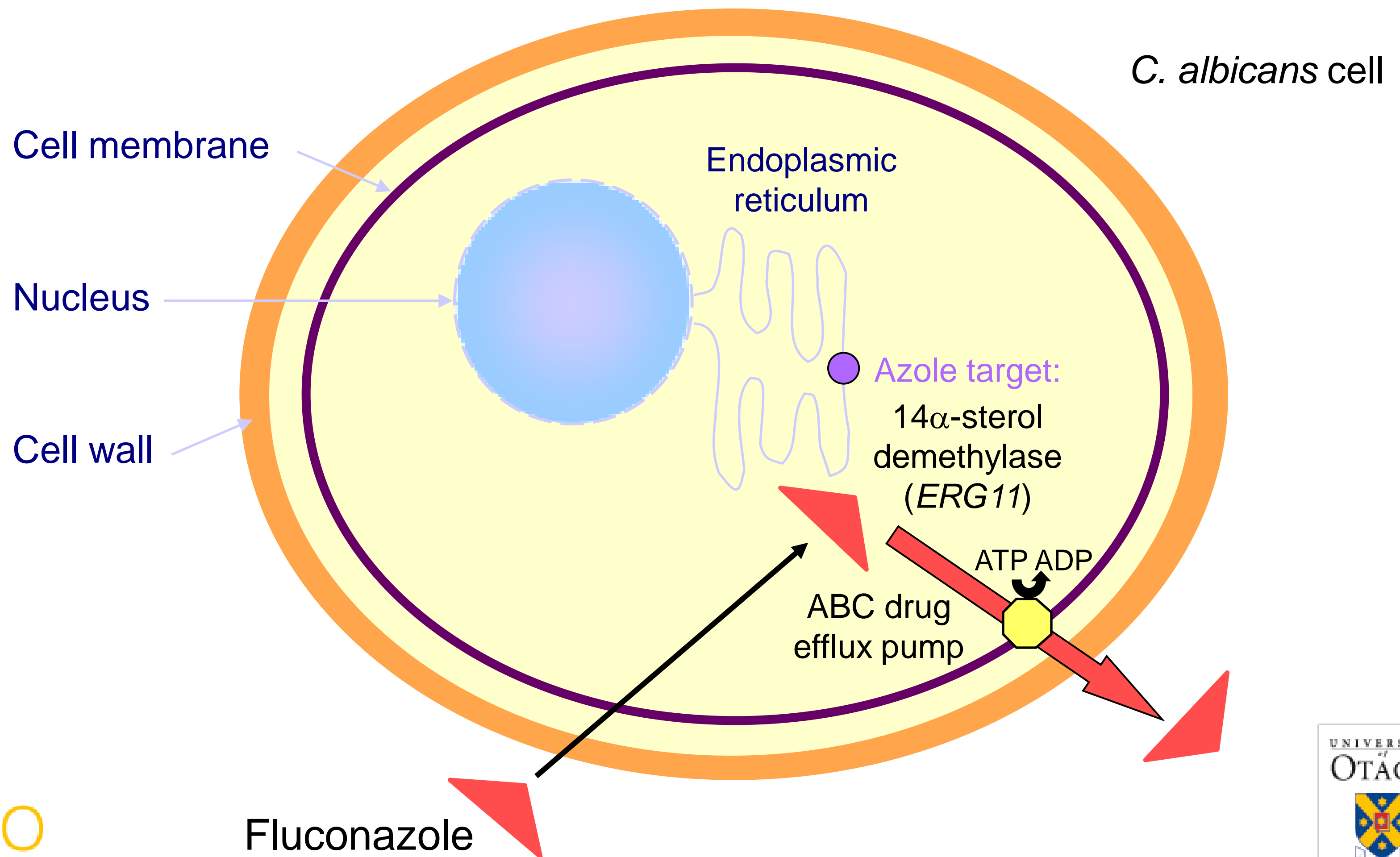
High level azole resistance in clinical isolates is due to energy dependent drug efflux



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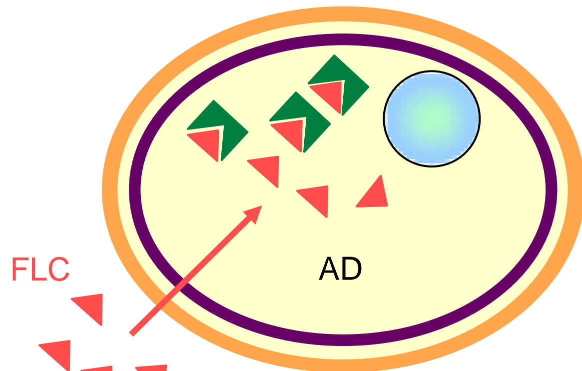
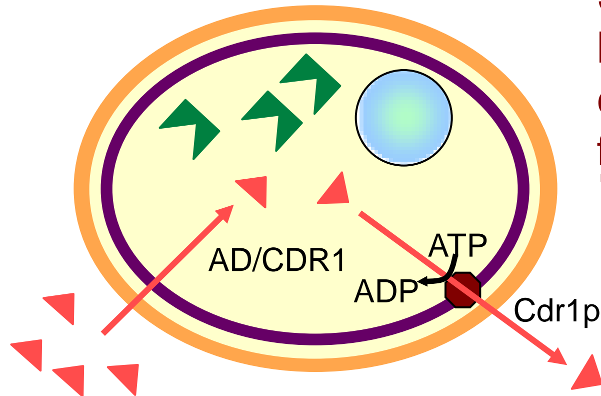
Otago's Strategy



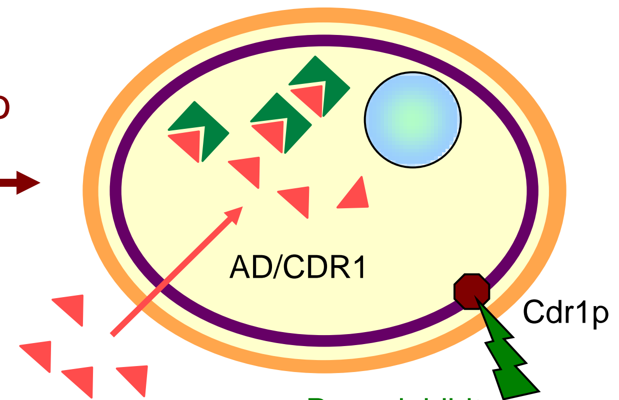
We have used the expression system to identify pump inhibitors that sensitise fluconazole-resistant cells to fluconazole

Host strain *S. cerevisiae* AD is very susceptible to fluconazole (FLC)

Screen a combinatorial library for components that chemosensitise AD/CDR1 to fluconazole



AD/CDR1, expressing Cdr1p, is highly **resistant** to fluconazole



AD/CDR1 rendered **susceptible** to fluconazole

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Overcoming Azole resistance

- Inhibition of azole efflux pumps “chemosensitizes” resistant fungal pathogen to azole drug
- **Efflux pumps inhibitor + azole = “Super-Azole”**
- Inhibition of all involved efflux pumps
- Specific inhibition of efflux pumps only – toxicity/safety profile
- Otago’s membrane protein expression system for screening
- “Super-Azoles”: efficacy and potency in clinical isolates confirmed; further (pre-)clinical development under way

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Drug Development Value Chain

Validated target (MoA)
Screening system
Compound identification

→

Clinical relevance
Efficacy, PK/PD
in vitro and *in vivo*
toxicity/safety in animal

→

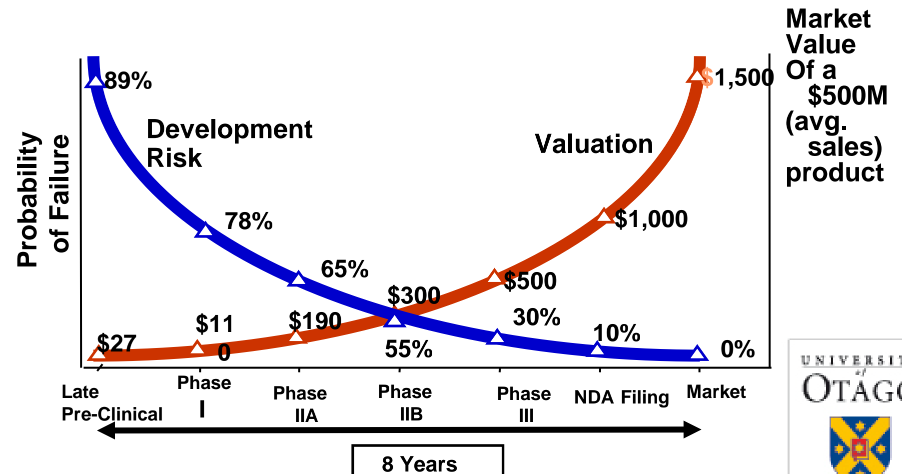
Pre-clinical tox/safety in humans
IND to enter clinical trials
Clinical trials phase I/II

in vivo proof of concept animal

1. valuation point

clinical proof of concept human

2. valuation point:



Slide kindly provided by David C. U'Pritchard
President, Druid Consulting LLC

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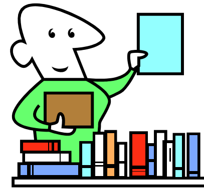
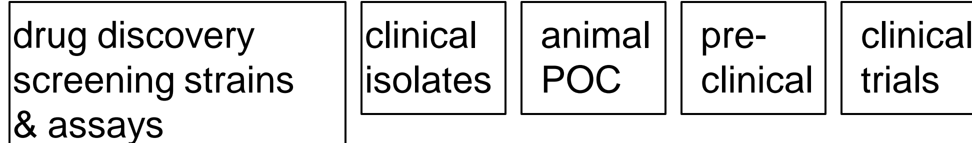
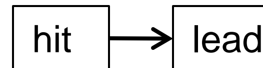
Aligning bench top and clinic





Scientific approach

Overcoming efflux-mediated azole resistance via specific pump inhibition in pathogen (Candida): inhibitor + azole drug = "Super-Azole"



"Super-Azole" label

1. Indication and usage: for the treatment of patients with Candida infections
-- including azole resistant Candida strains
-- including C. glabrata infections
-- including infections unresponsive to one or more azoles

2. Dosage and administration
3. Dosage forms and strengths
4. Contraindications (…)
7. Drug interactions (…)
16. Patient counseling.

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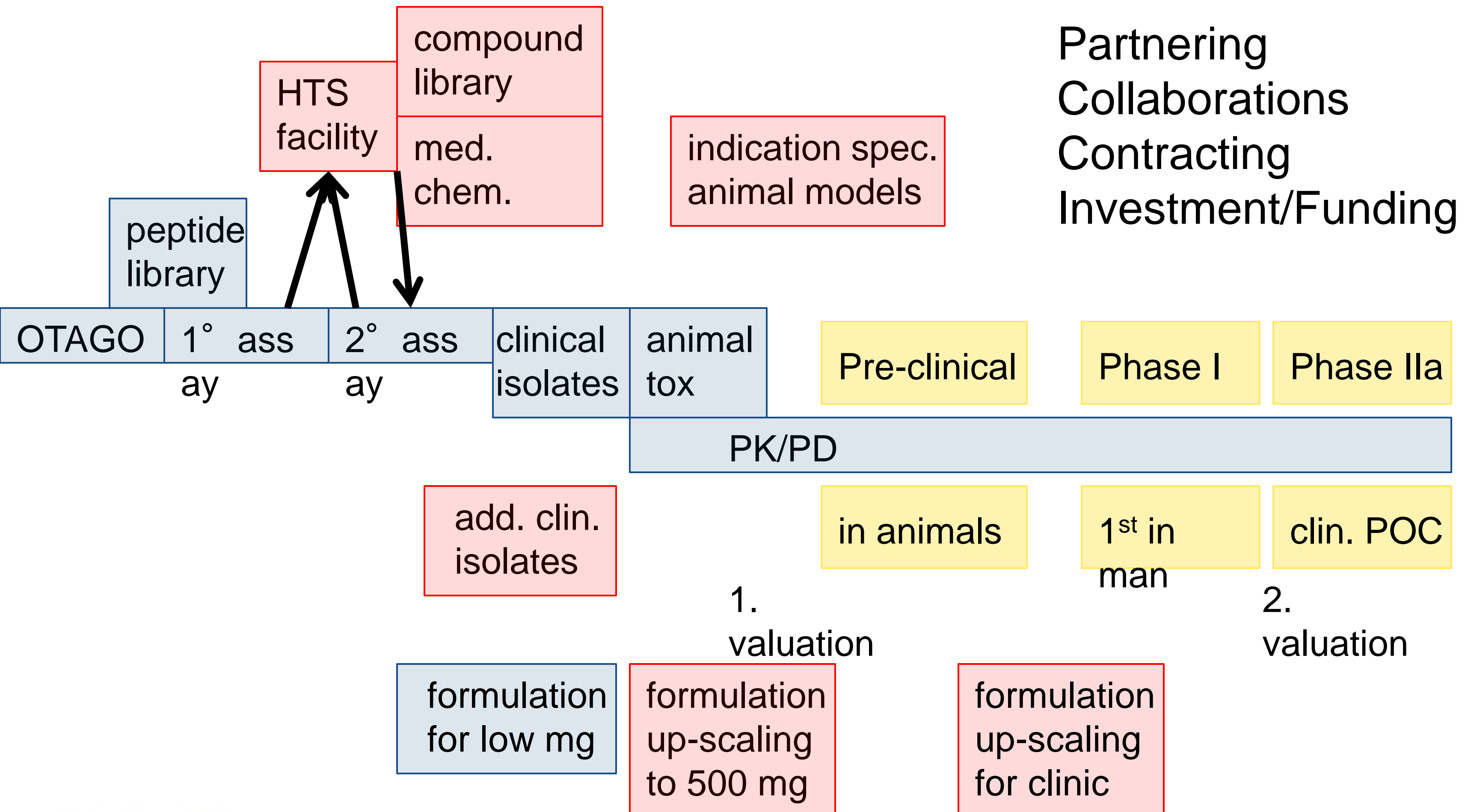
Severe candida infections (candidiasis)

- Increase of invasive candidiasis between 2000-2005
  - US: 50%
  - Queensland, Australia: 250%
- Mortality: 40-60%
- Excess length of stay: 5-10 days in ICU and up to 30 days in hospital
- Excess cost per episode: US$ 44,000
- Most frequent pathogen:
  - *Candida albicans* (50%);
  - *C. glabrata, C.tropicalis, C. parapsilosis* (each 15-30%);
  - *C. krusei* (1%)
- Recent increase of non-albicans candida infections by *C. glabrata* and *C. krusei*
- Patients on fluconazole prophylaxis: high risk of infection by fluconazole resistant *C. glabrata* and *C. krusei*

Fit with medical practice in the clinic

- Prophylaxis (posaconazole or fluconazole) for patients with elevated risk for severe fungal infection
  - Hematological: neutropenia, cellular immunodeficiency (leukemia, lymphoma, AIDS, etc.)
  - Iatrogenic: chemotherapeutics, antibiotics, catheters, surgery
- Diagnosis is still very challenging (bacterial vs fungal pathogen; PCR; microbiology- takes time, in particular susceptibility testing with isolated pathogen)
- Empirical therapy (according to protocol) and change with lab results or with observed sub-optimal response
- Fluconazole is often preferred treatment, but problematic for resistant Candida infections, in particular for *C. glabrata* and *C. krusei*

What we are looking for



Partnering
Collaborations
Contracting
Investment/Funding

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Current (growing) Otago Team

- **Professor Richard Cannon, Dr Brian Monk, Dr Kyoko Niimi, Dr Masa Niimi, Dr Ann Holmes, Dr Erwin Lamping, Dr Mikhail Kenyia**
  Fungal drug discovery team and inventors
  Molecular Microbiology Laboratory
  Department of Oral Sciences, University of Otago
- Professor Ian Tucker and Professor Stephen Duffull
  School of Pharmacy, University of Otago
- Professor Paul Glue MBChB (Otago); MD (Bristol); MRCPsych
  School of Medicine, University of Otago
- Professor Steve Chambers MBChB; MD; MSc; FRACP; Clin. Dir. of Infectious Diseases
  Pathology, University of Otago, Christchurch
- Dr Alex Tickle
  Commercialisation Manager
  Otago Innovation

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