Australia Biotech Invest 2016

Julie Phillips, Managing Director

26 October 2016

Opal Biosciences Limited is an innovative player in infectious disease treatment. An Australian biotechnology company committed to tackling a serious global health threat.

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IN THE HEADLINES

The Washington Post

The superbug that doctors have been dreading just reached the U.S.

THE HUFFINGTON POST
INFORM • INSPIRE • ENTERTAIN • EMPOWER

Why Is Multidrug-Resistant TB A Health Security Threat?

Tuberculosis is a public health crisis.

10/13/2016 10:24 am ET | **Updated** Oct 13, 2016

BBC NEWS

'Super-gonorrhoea' outbreak in Leeds

Medical Daily

Meet Candida Auris, The Drug-Resistant Yeast Infection That Kills Up To 60% Of Those Infected

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HIGH-LEVEL MEETING ON ANTIMICROBIAL RESISTANCE

21 SEPTEMBER 2016, UN HEADQUARTERS, NEW YORK

“Antimicrobial resistance poses a fundamental threat to human health, development, and security … We are running out of time.”

Dr. Margaret Chan, Director-General of WHO

21 September 2016, NEW YORK

Media release following UN General Assembly

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WHAT HAPPENS IF WE FAIL TO ACT?

NOW

23,000 people die yearly from antibiotic resistant bacterial infections in the U.S. and more than **2 million fall ill**, according to the Centers for Disease Control.

(ref http://www.cdc.gov/drugresistance/threat-report-2013/)

By 2050…

An average of 10 million people will die every year and it could cost the global economy up to $100 trillion.

(J. O'Neill: Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations, Dec 2014)

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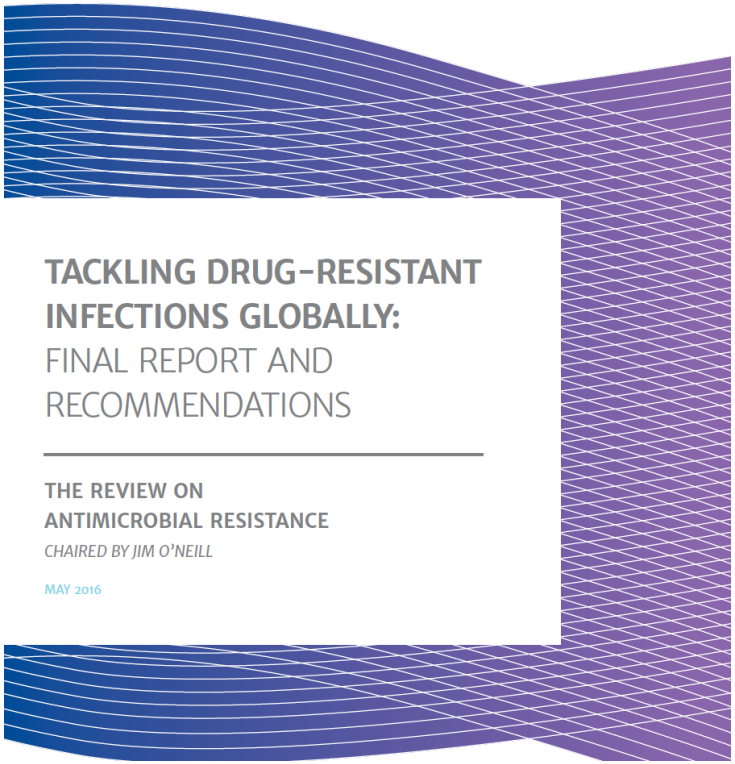
Review on Antimicrobial Resistance

Tackling drug-resistant infections globally



"We must increase the supply of new antimicrobials effective against drug-resistant bugs"

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GLOBAL HEALTH CHALLENGES

Rising antibiotics resistance, a threat to healthcare systems worldwide

Few new drugs, the antibiotics pipeline is running dry

Hard-to-treat fungal infections problematic for patients with weak immune systems

Increase in prevalence, due to factors such as climate change

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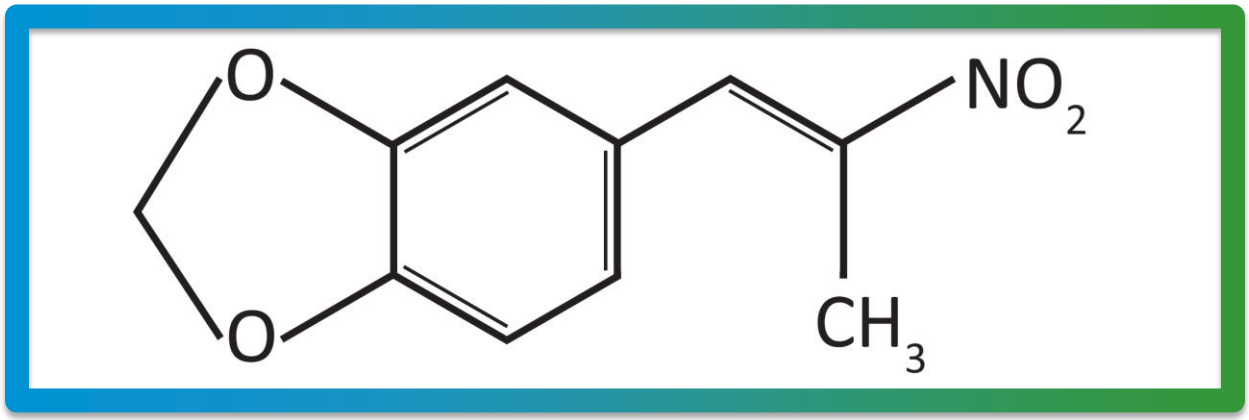
OPAL TECHNOLOGY



- **Opal Technology** has demonstrated activity against a wide range of human disease causing germs.
- Potential to combat dangerous superbugs
- Being assessed as a bioterrorism counter-measure
- Potential applications: injections, eye drops, tablets, creams

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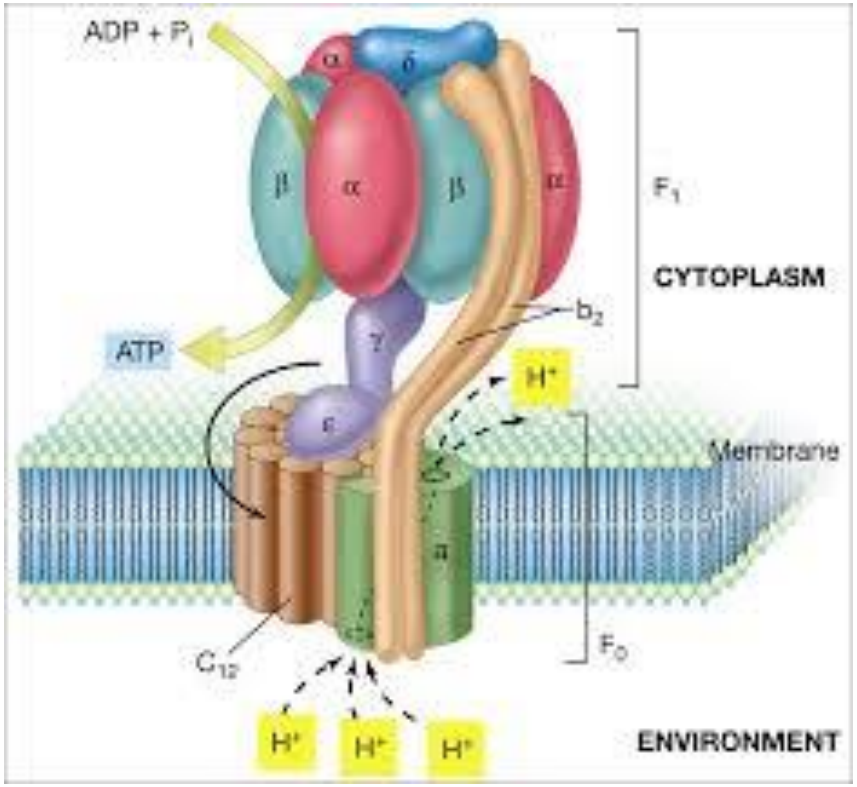
TARGETING ATP SYNTHESIS?



ATP Synthase may be the primary (indirect) target

ESKAPE Pathogens:

Enterococcus faecium (VRE)

Staphyloccoccus aureus (MRSA)

Other G-ve:

Neisseria gonorrhoea

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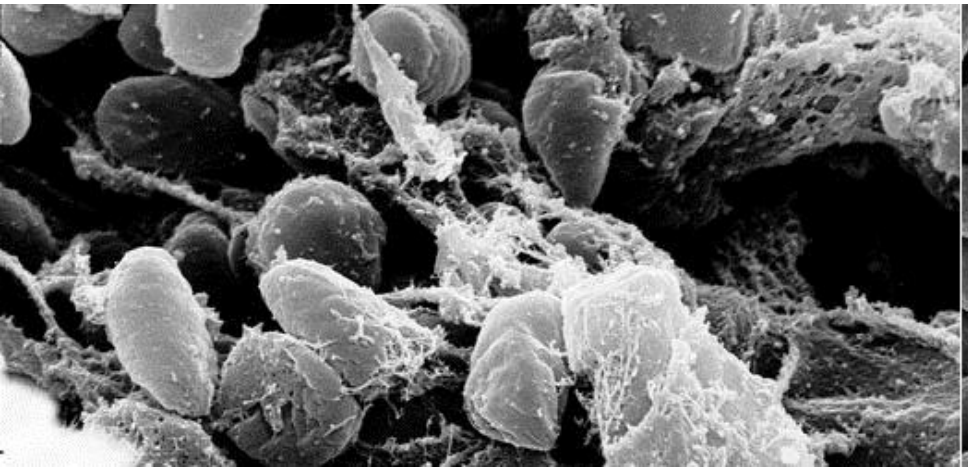
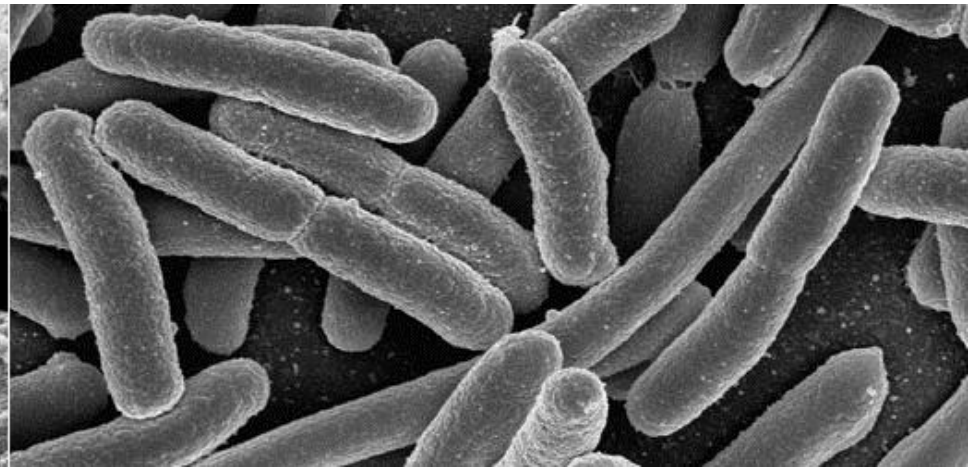
BIOTERRORISM COUNTER-MEASURE

Opal Technology – screened as a potential **biological weapons counter-measure** by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID).





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NIAID/USAMRIID PROGRAMS

*Drug resistant Tuberculosis**

Pneumocystis

Biowarfare target

*These projects have been funded with Federal funds from the NIH/NIAID/DMID
** Contract No. HHSN272201100012I
*** Contract No. HHSN272201100018I
**** Contract No. HHSN272201000029I / HHSN27200002 /A51
#This project has been supported by the U.S. Army Medical Research Institute of infectious

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Antifungal and Antipneumocystis Activity of the Investigational Antimicrobial BDM-I

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ABSTRACT

Background: There is a critical need for the development of new antimicrobials with broad-spectrum activity. In an initial screen, the novel antimicrobial agent BDM-I demonstrated broad-spectrum activity against both fungi and bacteria. Our objective was to further evaluate the in vitro antifungal and antipneumocystis activity of BDM-I against select fungi, including causative agents of opportunistic and endemic mycoses.

Methods: Clinical isolates, including *Cryptococcus* species, *Candida glabrata*, *Blastomyces dermatitidis, Coccidioides* species, and *Histoplasma capsulatum*, were evaluated. MICs were determined using CLSI reference methods for yeasts (M27-A3) and filamentous fungi (M38-A2). Antipneumocystis activity was measured using a well-described ATP luciferin-luciferase reaction assay, and the IC50 of BDM-I was determined against *P. carinii* and *P. murina*. Mammalian cell toxicity was also measured using the ATP assay in the human lung carcinoma cells (A549) and the rat lung fibroblasts (L2).

Results: BDM-I demonstrated potent activity against endemic fungi, including *B. dermatitidis, Coccidioides* species, and *H. capsulatum* (MIC90 range 0.25 – 0.5 µg/ml at 100% growth inhibition). Similarly, activity was also observed against *C. neoformans* and *C. gattii* (MIC90 2 µg/ml at 100% growth inhibition) as well as *C. glabrata* (MIC90 2 µg/ml). BDM-I also had marked activity against *P. carinii* and *P. murina* (IC50 on day 3 of exposure <0.1 and 0.174 µg/ml, respectively). While toxicity was observed against the L2 cell line (IC50 <0.1 µg/ml), the antipneumocystis activity was 30 times lower than that observed against the A549 cell line (IC50 0.174 vs. 5.26

Fungal Species	*Cryptococcus neoformans* (N= 13)	*Cryptococcus gattii* (N = 10)	*Candida glabrata* (N = 10)	*Blastomyces dermatitidis* (N = 10)	*Coccidioides species* (N = 10)	*Histoplasma capsulatum* (N = 10)
50% Inhibition Endpoint (µg/ml)						
MIC Range	0.25 – 2	1 – 2	0.5 – 1	0.06 – 0.125	0.125 – 0.25	< 0.03 – 0.25
MIC50	1	2	1	0.125	0.25	0.06
MIC90	2	2	1	0.125	0.25	0.25
GM MIC	1.00	1.74	0.81	0.09	0.22	0.05
100% Inhibition Endpoint (µg/ml)						
MIC Range	2	2	1 – 2	0.125 – 0.25	0.25	0.03 – 0.5
MIC50	2	2	1	0.25	0.25	0.125
MIC90	2	2	2	0.25	0.25	0.5
GM MIC	2.00	2.00	1.15	0.20	0.25	0.9

BACKGROUND

- The development of novel antimicrobial agents is of critical importance due to evolving antimicrobial resistance.
- BDM-I (**Figure 1**) is a novel antimicrobial agent currently under development by BioDiem Ltd., who has a Non-Clinical Evaluation Agreement with the NIH/NIAID for the pre-clinical evaluation of this investigational agent.
- In initial screens, BDM-I demonstrated broad-spectrum activity against both fungi and bacteria.

OBJECTIVE

Our objective was to further evaluate the in vitro antifungal and antipneumocystis activity of BDM-I against select fungi. This included causative agents of opportunistic and endemic mycoses and *Pneumocystis* species. In addition, the potential for mammalian cell toxicity was also evaluated.

MATERIALS AND METHODS

Isolates

- Clinical isolates of *Cryptococcus neoformans* and *Cryptococcus gattii, Candida glabrata*, *Blastomyces dermatitidis, Coccidioides* species, and *Histoplasma capsulatum*, were obtained from the Fungus Testing Laboratory at the UT Health Science Center at San Antonio.
- Isolates of *Pneumocystis carinii* and *Pneumocystis murina* were maintained at the Cincinnati Foundation for Biomedical Research and Education.

Antifungal Activity

- In vitro antifungal activity was measured according to the CLSI M27-A3 and M38-A2 guidelines. These assays are performed in the Fungus Testing Laboratory at the UT Health Science Center at San Antonio.
- After the appropriate period of incubation (24 to 48 hours for *Candida glabrata*, 72 hours for *Cryptococcus* species, and 72 – 96 hours for *Blastomyces dermatitidis, Coccidioides* species, and *Histoplasma capsulatum*) the MIC values were determined.
- Two MIC values were used: 1) the concentration resulting in a prominent reduction in growth (50% of the growth control), and 2) the concentration resulting in complete inhibition of growth (optically clear well).
- The MICs that inhibited 50% and 90% of the fungi (MIC50 and MIC90, respectively), and the geometric mean (GM) MICs were determined.

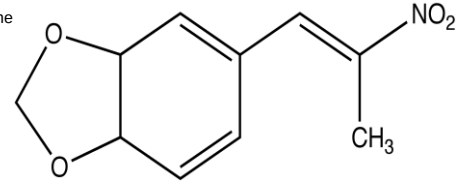
Antipneumocystis Activity

- Antineumocystis activity was measured against *P. carinii* and *P. murina*. This work was performed at the Cincinnati Foundation for Biomedical Research and Education.
- For each study, a set of controls was included: 1) growth control (untreated *Pneumocystis*); 2) pentamidine at 0.3 or 1 µg/ml; 3) ampicillin at 10 µg/ml; 4) media control or vehicle control (at the highest concentration used). Plates are incubated at 37°C with 5% CO_2 in a water-jacketed incubator.
- At 24, 48, and 72 hours, 50 µl samples were removed for ATP analysis.
- Antipneumocystis activity was measured using an ATP assay (ATPlite luminescence ATP Detection Assay, Perkin Elmer), which is based on the release of bioluminescence driven by ATP in the luciferin-luciferase reaction.
- Activity was classified by the IC50 value as highly active (<0.010 µg/ml), very marked (0.011 - 0.099 µg/ml), marked (0.10 – 0.99 µg/ml), moderate (1.0 – 9.99 µg/ml), slight (10.0 – 49.9 µg/ml), or inactive (≥ 50 µg/ml).

Mammalian Cell Toxicity

- The ATP assay described above was used to evaluate the viability of cell monolayers in order to assess for potential toxicity to mammalian cells.
- Confluent monolayers consisted of the human lung cell carcinoma cell line A549 (ATCC CCL-185) and the rat lung fibroblast line L2 (ATCC CCL149).

Figure 1. Chemical structure of the novel antimicrobial agent BDM-I.



CONCLUSIONS

The novel antimicrobial agent BDM-I demonstrated in vitro activity against *Cryptococcus neoformans* and *Cryptococcus gattii* as well as the endemic fungi *Blastomyces dermatitidis, Coccidioides immitis/posadasii*, and *Histoplasma capsulatum.* This investigational agent also demonstrated marked activity against both *Pneumocystis carinii* and *Pneumocystis murina*. Although toxicity was observed against the rat lung fibroblast line L2, the antipneumocystis activity was 30 times lower than that observed against the human lung cell carcinoma cell line A549. Further studies are warranted to determine the potential of this broad-spectrum antimicrobial agent.

RESULTS (cont.)

Table 1. MIC ranges, MIC50, MIC90 and GM MIC values for BDM-I versus *Cryptococcus* species and endemic fungi.

Parameter	*Cryptococcus neoformans* (n = 13)	*Cryptococcus gattii* (n = 10)	*Blastomyces dermatitidis* (n = 10)	*Histoplasma capsulatum* (n = 10)	*Coccidioides* spp. (n = 10)
50% Inhibition Endpoint					
MIC Range	0.25 - 2	1 - 2	0.06 - 0.125	≤ 0.03 - 0.25	0.125 - 0.25
MIC50	1	2	0.125	0.06	0.25
MIC90	2	2	0.125	0.25	0.25
GM MIC	1.00	1.74	0.09	0.05	0.22
100% Inhibition Endpoint					
MIC Range	2	2	0.125 - 0.25	0.03 - 0.5	0.25
MIC50	2	2	0.25	0.125	0.25
MIC90	2	2	0.25	0.5	0.25
GM MIC	2.00	2.00	0.20	0.09	0.25

Table 2. Antipenumocystis activity of BDM-I as measured by percent reduction in ATP.

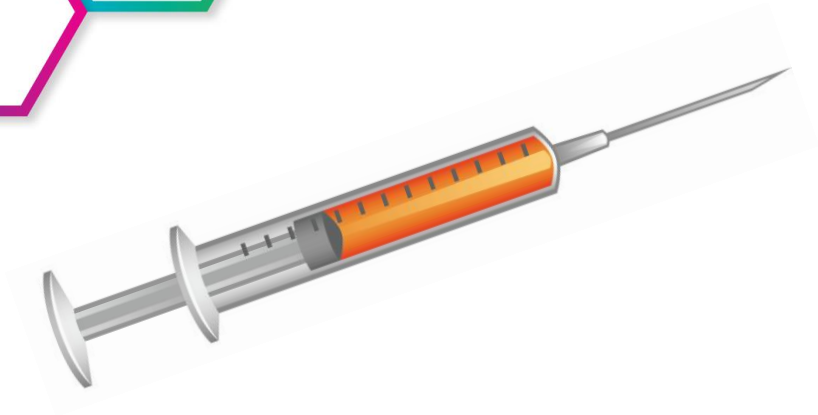
Species	*Pneumocystis carinii*			*Pneumocystis murina*		
Time Point	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Media	0	2.04	0.84	0	0	12.18
Ampicillin 10µg/ml	0	0	0	0	0	12.73
Pent. 1 µg/ml	75.69	96.03	83.08	78.99	78.22	71.83
BDM-I 100 µg/ml	97.30	95.74	91.92	98.85	98.76	98.77
BDM-I 10 µg/ml	96.45	96.81	92.76	97.81	99.03	98.47
BDM-I 1 µg/ml	53.55	90.35	90.16	63.18	98.90	97.71
BDM-I 0.1 µg/ml	34.76	10.27	73.08	26.39	21.08	21.68
BDM-I IC50 (µg/ml)	0.047	0.411	< 0.1	0.441	0.172	0.174

Table 3. Toxicity to mammalian cells as measured by percent reduction in ATP.

	A549 Cell Line				L2 Cell Line			
Agent	Day 1	Day 2	Day 3	Day 4	Day 1	Day 2	Day 3	Day 4
Antimycin A 75 µg/mL	26.79	79.34	72.56	94.85	76.37	49.59	61.84	83.05
BDM-I 100 µg/mL	99.36	99.72	99.71	99.66	99.30	99.41	99.20	99.70
BDM-I 10 µg/mL	11.50	31.28	52.95	39.47	99.42	99.26	99.62	99.66
BDM-I 1 µg/mL	11.17	10.48	11.77	19.85	99.15	97.19	99.59	97.08
BDM-I 0.1 µg/mL	8.06	7.87	7.46	7.07	80.37	62.54	40.30	47.16
IC50 (µg/ml)	13.70	8.45	5.26	6.09	< 0.1	< 0.1	< 0.1	< 0.1

This project has been funded with Federal funds from the NIH/NIAID/DMID Under Contract No. HHSN272201100018I.
BDM-I drug-substance was provided by BioDiem Ltd., Melbourne, Australia.

POTENTIAL PRODUCT LINE



Intravenous Use (Injection)

Aimed at: Fungal infections in the bloodstream, lungs and other body cavities e.g. sinuses. And bacterial infections that cause blood poisoning, urinary tract infections and pneumonia.

Topical Use (Cream, ointment, spray)

Aimed at: Skin, soft tissue and mucous membrane infections, such as tinea, conjunctivitis and external ear infections, along with burns.

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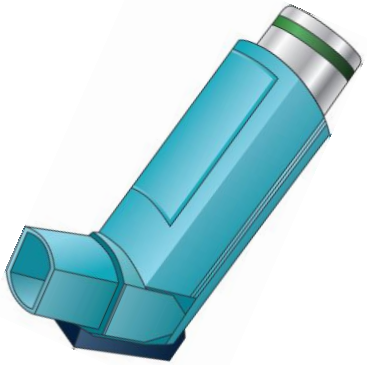
POTENTIAL PRODUCT LINE

Oral Use (Tablets, capsules, syrup, mouthwash)

Aimed at: Germs that cause gut infections such as gastroenteritis.



Lung (Inhalation)

Aimed at: Chronic diseases such as cystic fibrosis where lung infection is a major cause of illness and death.

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OPAL'S DEVELOPMENT PLAN

With an international team and development plan in place, Opal Biosciences Limited is seeking investment to progress its technology.

- Opal-I, injectable product
- Opal-T, topical product
- Opal-L, pulmonary delivery

Our commercial objective is to out-license or sell the technologies near term to a larger pharmaceutical company for clinical trials and marketing.

OPAL'S INFECTION TARGETS (examples)

Infection	Cause (Microorganism)	BDM-I activity (*in vitro*)
Fungal infection	*Scedosporium prolificans, Aspergillus fumigatus*	✔
Tuberculosis	*Mycobacterium tuberculosis** (including resistant TB)*	✔
URTI and LRTI	*Pneumocystis (carinii)** Haemophilus influenza*	✔
STI	*Neisseria gonorrhoea, Candida spp, T. Vaginalis*	✔
GIT	*Campylobacter jejunii*	✔
Invasive, urogenital	*Candida glabrata*	✔

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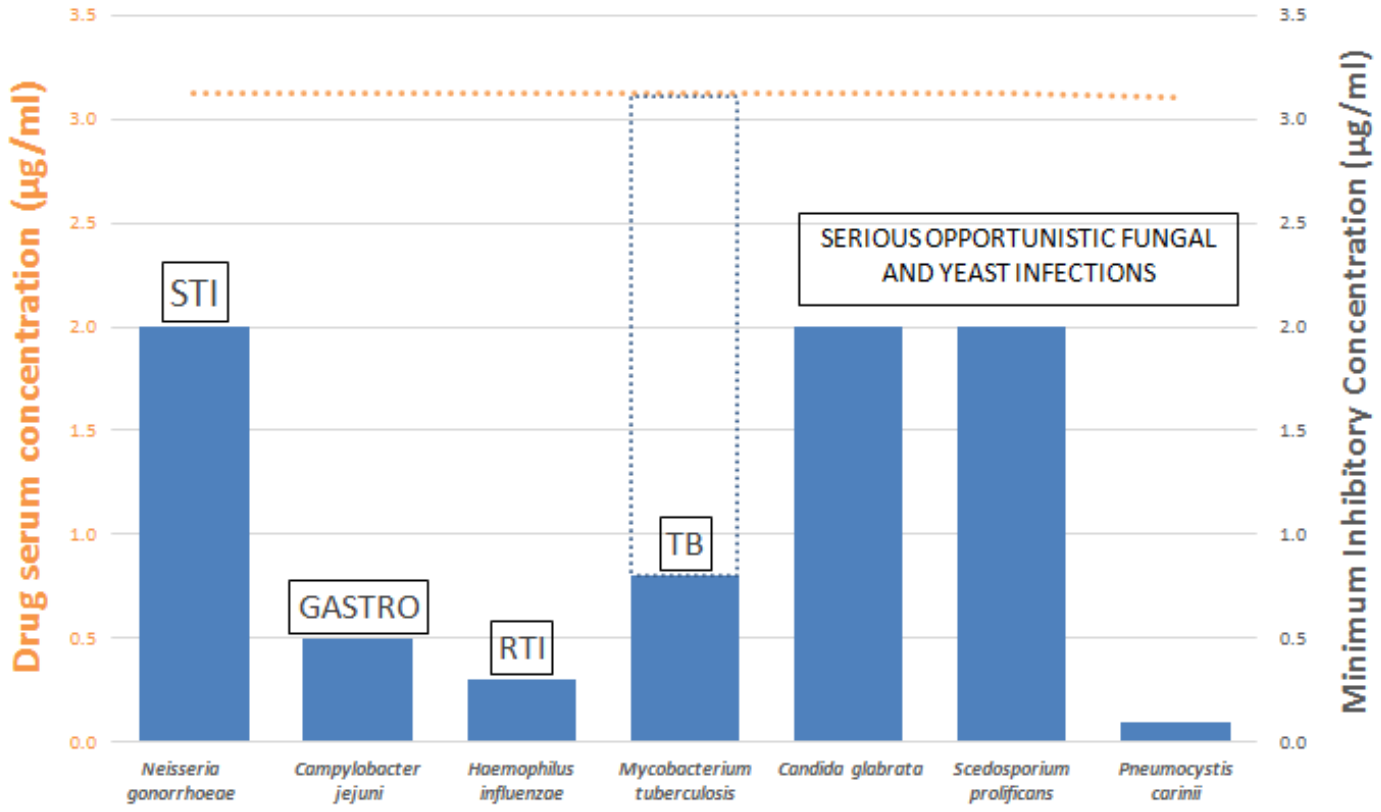
MIC's vs DRUG LEVEL (examples)



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MARKET SIZE

Global antifungals market, US$14.5 billion by 2020

Global antibacterials market, US$38.9 billion by 2023

Global anti-infectives market, US$111.4 billion by 2024

Ref: Global Antifungal Drugs Market Analysis 2016 Forecasts to 2021 – September 2016 – Wise Guy Reports.
Anti-infectives Market Anaylsis by Type and Segment Forecast to 2024 – July 2016 – Grand View Research Industry Report.
Antibacterial Drugs Market- A Global Industry Analysis, Size, Share, Growth, trends and Forecast, 2015-2023, Transparency Market Research, July 2015.

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INVESTMENT POTENTIAL

- Anti-infectives market large and growing
- Few competitors in development
- Government incentives in place
- Major pharmas returning to the sector and buying innovation
- Opal Technology's potential
- Experienced international team

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US GOVERNMENT INCENTIVES

1. **The GAIN (Generating Antibiotic Incentives Now) Legislation**
2. **FDA's Priority Review**: FDA's goal is to take action on an application within 6mths (compared to 10mths).
3. **Orphan Drug Designation**: Sponsor of the drug entitled to development incentives (tax credits, extended market exclusivity).
4. **FDA's Fast Track Process**: Designed to facilitate the development, and expedite the review of much needed new treatments.

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GLOBAL COLLABORATIONS

The Opal Technology project brings together a wealth of expertise.

Griffith UNIVERSITY

THE UNIVERSITY OF SYDNEY

FORMulytica®

MONASH University

University of Western Sydney

National Institute of Allergy and Infectious Diseases

USAMRIID
United States Army Medical Research Institute of Infectious Diseases

http://www.niaid.nih.gov/LabsAndResources/resources/dmid/invitro/Pages/invitro.aspx
http://www.niaid.nih.gov/labsandresources/resources/dmid/animalmodels/Pages/default.aspx

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