Activity of Cysteamine against the Cystic Fibrosis Pathogen *Burkholderia cepacia* Complex

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There are no wholly successful chemotherapeutic strategies against *Burkholderia cepacia* complex (BCC) colonization in cystic fibrosis (CF). We assessed the impact of cysteamine (Lynovex) in combination with standard-of-care CF antibiotics *in vitro* against BCC CF isolates by the concentration at which 100% of bacteria were killed (MIC$_{100}$) and checkerboard assays under CLSI standard conditions. Cysteamine facilitated the aminoglycoside-, fluoroquinolone- and folate pathway inhibitor-mediated killing of BCC organisms that were otherwise resistant or intermediately sensitive to these antibiotic classes. Slow-growing BCC strains are often recalcitrant to treatment and form biofilms. In assessing the impact of cysteamine on biofilms, we demonstrated inhibition of BCC biofilm formation at sub-MIC$_{100}$s of cysteamine.

Colonization of the airways with *Burkholderia cepacia* complex (BCC) is a major contributory factor to patient morbidity and mortality in cystic fibrosis (CF) (1–3), reducing life expectancy of those affected (4%) of the adult CF population) by as much as 16 years (2, 4). Most, if not all, BCC strains (5) are clinically resistant or inherently insensitive to currently available CF antibiotics (2, 6, 7). BCC colonization is a significant clinical challenge in CF that will increase as survival rates for this condition continue to improve (8, 9). There remains a critical, unmet need for new chemotherapeutic approaches to resolving BCC colonization in CF.

We previously described the antimicrobial, antifibolm, and mucolytic attributes of cysteamine against *Pseudomonas aeruginosa* and other CF bacterial pathogens (10–12) and report here that, more strikingly, the modification of currently available therapeutic strategies (2, 13) with the introduction of cysteamine as an adjunct antimicrobial agent brings about effective killing of BCC (both type strains and CF isolates).

### MATERIALS AND METHODS

**Bacterial strains and reagents.** The 36 *Burkholderia* strains employed for this study include representative strains from each species (or genomovar), including *B. cenocepacia* and *B. multivorans*, those most commonly associated with infection in cystic fibrosis (14). Sixteen of the BCC clinical isolates were sourced from Aberdeen Royal Infirmary, with seven from adult patients and nine pediatric isolates. Eight strains were sourced from the Glasgow adult patient cohort. An additional 12 type strains were included in this study. Cysteamine, trimethoprim, sulfamethoxazole, and tobramycin and ceftazidime were sourced from Discovery Fine Chemicals (NovaBiots Ltd., Craibstone, Bucksburn, Aberdeen, United Kingdom). All other reagents were purchased from Sigma-Aldrich (United Kingdom). MIC and checkerboard assays. The concentration at which 100% of bacteria were killed (MIC$_{100}$) for all BCC isolates was determined for cysteamine and the antibiotics tobramycin, ciprofloxacin, ceftazidime, and trimethoprim-sulfamethoxazole using the CLSI broth microdilution procedure (15). Checkerboard assays of cysteamine and antibiotics were conducted according to the method of Burkhart et al. (16). Antibiotic susceptibility profiling of BCC (resistant, intermediate, or sensitive to antibiotics) was performed using CLSI performance standards for antimicrobial susceptibility testing using interpretive standards for other non-Enterobacteriaceae (17).

**Biofilm assays.** The crystal violet method for detecting the adherence of bacterial biomass to polypropylene 96-well plates was adapted from similar studies (18–20). Inocula were prepared using a McFarland standard equivalent of $5 	imes 10^7$ CFU/ml from growing cultures (according to CLSI document M07-A9 [15]) into 100 µl of cation-adjusted Mueller-Hinton broth containing appropriate concentrations of test antibiotic. Cultures were incubated statically for 48 h in a humidified atmosphere at 37°C to establish biofilms. Culture medium containing planktonic bacteria was carefully removed and discarded, and the plates were washed gently three times with 150 µl of sterile phosphate-buffered saline (PBS) prior to air drying for 1 h. The remaining attached bacteria in wells were then stained with 200 µl of 1% crystal violet solution for 2 min, prior to 3 further washes with PBS and solubilization with 200 µl of ethanol. Plates were then read at 595 nm.

Assessment of cysteamine-mediated biofilm prevention in a shear-flow environment was performed using a BioFlux 200 automated microfluidic system (Fluxion Biosciences, CA). Inocula were prepared as described above (CLSI document M07-A9 [15]) from growing cultures and seeded into prewarmed cation-adjusted Mueller-Hinton broth with or without the sub-MIC$_{100}$ concentration of 128 µg/ml of cysteamine. A 48-well Bioflux plate was primed for 1 min with prewarmed cation-adjusted Mueller-Hinton broth prior to addition of treated and untreated cultures. Medium was passed through capillaries at 37 µl/h (0.4 dyne) for 20 h, and images were captured using an Axiovert 40CFL microscope (Carl Zeiss, United Kingdom) and camera and Bioflux 200 software.

**RESULTS**

MIC assays with combinations of cysteamine and the recommended CF antibiotics were performed to assess the utility of cysteamine *in vitro* as an adjunct antibiotic therapy against BCC. A panel of BCC clinical isolates and type strains was tested to deter-
In addition to this impact on widely used antibiotics, the ability of cysteamine to enhance the activity of ceftazidime and trimethoprim-sulfamethoxazole, antibiotics used specifically to treat BCC, was also investigated (Tables 3 and 4). Interestingly, and pointing to an antibiotic class-specific effect, cysteamine had no major impact on ceftazidime susceptibility of the BCC strains tested in this system. In contrast, cysteamine potentiated the activity of trimethoprim-sulfamethoxazole against the majority (22 out of 36) of BCC isolates and type strains studied.

Planktonic cells were employed in our initial cysteamine adjunct assays, whereas in vivo, BCC colonizes the CF airway in biofilm form (21, 22). We have already described the antibiofilm properties of cysteamine against *Pseudomonas* (10–12). In order to confirm any activity of cysteamine specifically against BCC biofilm structures in vitro, we assessed its ability to prevent BCC biofilm formation using the Bioflux microfluidic system, and we used the crystal violet method for assessing biofilm mass in 96-well microtiter plates. In both systems, the
methodology was adapted to keep conditions as close as possible to CLSI standards for MIC testing rather than to favor the growth of biofilms. For example, the medium used was cation-adjusted Mueller-Hinton broth as opposed to other choices, such as tryptic soy broth, which would favor biofilm formation in BCC (23). This was to clearly demonstrate inhibition of attachment at sub-MIC100s. Crystal violet assessment demonstrated inhibition of bacterial attachment at 48 h in the presence of concentrations of cysteamine subinhibitory for planktonic growth (Fig. 1). Inhibition of biofilm formation was dose dependent, increasing with concentrations of cysteamine approaching the MIC, with significant inhibition of both strains of \textit{B. cenocepacia} tested at 128 μg/ml. The antibiofilm activity of cysteamine against BCC was confirmed in real time in a dynamic-flow microfluidics system. The effect of a subinhibitory concentration of cysteamine was assessed on biofilm formation in the BioFlux microfluidic system on \textit{B. cenocepacia} clinical strain CFSYN 1112. Cysteamine prevented biofilm formation in cells in channels that were exposed to cysteamine over 20 h compared to samples in wells not exposed to cysteamine (see Movie S1 in the supplemental material). Viable planktonic cells from the outlet well were cultured at the end of the experiment, confirming an effect on attachment and not bacterial viability at the test concentration.

**DISCUSSION**

The findings of our current study point to the potential of cysteamine as a means to resolve or prevent BCC colonization through a simple and sustainable modification to the current standard of care in CF. Tobramycin and ciprofloxacin are mainstays of the CF antibiotic regimen, and resistance to these antibiotics in CF BCC strains is common and inherent in some strains (24) and is readily selected for (25); indeed, we demonstrate that all but one of the strains (NCTC 13008) tested in this study which had been isolated from a patient with CF were resistant to tobramycin treatment. Cysteamine was able to reverse the tobramycin and cipro-

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### TABLE 2 Antimicrobial activities of ciprofloxacin and ciprofloxacin in combination with cysteamine against \textit{Burkholderia} isolates

| Organism       | Strain       | Median MIC100 (μg/ml) of: | Ciprofloxacin (μg/ml) of combination | Ciprofloxacin S/I/R |
|----------------|--------------|----------------------------|--------------------------------------|--------------------|
|                |              | Lynovex       | Ciprofloxacin       | Lynovex alone     | Ciprofloxacin alone | Lynovex alone     | Ciprofloxacin alone | S/I/R   |
| \textit{B. cenocepacia} | NCTC 13008   | 128.00 1.00  | S                     | 128/1              | S                   |
| \textit{B. multivorans} | DSMZ 13243   | 256.00 1.0000 | S                     | 128/0.25           | S                   |
| \textit{B. dolosa} | DSMZ 16088   | 256.00 16.00  | R                     | 256/16             | R                   |
| \textit{B. anithina} | DSMZ 16086   | 256.00 0.125  | S                     | 256/0.125          | S                   |
| \textit{B. ambifaria} | DSMZ 16087   | 256.00 0.25   | S                     | 256/0.125          | S                   |
| \textit{B. stabilis} | NCTC 13011   | 128.00 8.00    | R                     | 128/0.25           | S                   |
| \textit{B. cenocepacia} | DSMZ 16553   | 256.00 2.00    | I                     | 128/0.5            | S                   |
| \textit{B. cenocepacia} | NCTC 13417   | 256.00 2.00    | I                     | 128/0.5            | S                   |
| \textit{B. vietnamensis} | ATCC BAA-248 | 256.00 0.25    | S                     | 256/0.25           | S                   |
| \textit{B. pyrrocinia} | ATCC 15958   | 256.00 0.25    | S                     | 256/0.25           | S                   |
| \textit{B. vietnamensis} | 946          | 128.00 8.00    | R                     | 64/2               | I                   |
|                 | 888          | 256.00 4.00    | I                     | 128/2              | I                   |
| \textit{B. cenocepacia} | 1223         | 256.00 1.00    | S                     | 128/0.5            | S                   |
|                 | 1225         | 256.00 0.50    | S                     | 64/0.25            | S                   |
|                 | 1237         | 256.00 >32     | R                     | 256/2              | I                   |
| \textit{B. multivorans} | 1140         | 256.00 2.00    | I                     | 256/1              | S                   |
|                 | 1142         | >256 1.00      | I                     | 64/0.5             | S                   |
|                 | 1247         | >256 4        | I                     | 128/2              | I                   |
| \textit{B. cenocepacia} | CFSYN 936    | 128 32         | R                     | 64/4               | I                   |
|                 | CFSYN 1045   | 256 0.125      | S                     | 64/0.0625          | S                   |
|                 | CFSYN 1112   | 256 16         | R                     | 128/4              | I                   |
| \textit{B. cypacia} | CFSYN 946    | 128 4          | I                     | 64/2               | I                   |
| \textit{B. multivorans} | CFSYN 1081   | >256 2        | I                     | 256/0.5            | S                   |
|                 | CFSYN 954    | >256 8        | R                     | 256/4              | I                   |
|                 | CFSYN 945    | >256 16       | R                     | 256/16             | R                   |
| \textit{B. cypacia} | NCTC 10743   | >256 0.5      | S                     | 256/0.5            | S                   |
|                 | NCTC 10744   | 256 0.5       | S                     | 256/0.5            | S                   |
| \textit{B. multivorans (gen. II)} | 05.4136OrgB | 256 2         | I                     | 256/2              | I                   |
|                 | 05.38686OrgB | 256 0.0625    | S                     | 256/0.0625         | S                   |
| \textit{B. cenocepacia (gen. IIIA)} | 05.66335OrgA | 256 0.0625     | S                     | 256/0.0625         | S                   |
|                 | 02.37324OrgA | >256 0.25    | S                     | 256/0.125          | S                   |
| \textit{B. stabilis (gen. IV)} | 05.51979   | 256 0.125     | S                     | 128/0.125          | S                   |
|                 | 05.56937OrgA | 256 0.25      | S                     | 256/0.25           | S                   |
| \textit{B. vietnamensis (gen. V)} | 05.76464OrgC | 256 0.25      | S                     | 256/0.25           | S                   |
|                 | 07.24721OrgB | 256 0.5       | S                     | 128/0.25           | S                   |

All results represent the MIC100s from triplicate samples from triplicate experiments. S/I/R determination was based upon CLSI interpretive criteria. All data manipulation was carried out in Microsoft Excel. Resistant or intermediate results are highlighted with shading.
floxacin resistance phenotype and improve sensitivity to cotrimoxazole treatment (Tables 1 to 3). Therefore, cysteamine has the potential to extend the target spectrum of these antibiotics to include BCC. This is timely as regards its potential use as an adjunct to tobramycin considering the recent increased interest in the reapplication of inhaled or high-dose tobramycin against BCC (26, 27). Furthermore, the activity of antibiotics specifically deployed against BCC, such as trimethoprim-sulfamethoxazole, can also be further potentiated by cysteamine. Interestingly, ceftazidime activity was not altered by cotreatment with cysteamine, which suggests an antibiotic class-specific effect, at least within the in vitro systems employed in this study to assess antimicrobial activity.

The slow-growing, biofilm-forming characteristic of BCC contributes to the recalcitrance of this organism to existing antibiotic chemotherapy. In this study, we followed our previous work on the interactions of cysteamine with biofilm (10) in addition to assessing any direct antimicrobial activity. Cysteamine inhibited bacterial attachment at concentrations below the MIC$_{100}$ for each strain tested, with significant inhibition of B. cepacia type strain DSMZ 16553 and clinical isolate CFSYN 1112. Interestingly, although we previously demonstrated that combinations of tobramycin and cysteamine were more effective in biofilm prevention and eradication (data not shown). Cysteamine was not able to disrupt existing biofilms in the slower-growing BCC strains over 48 h over the same range of concentrations of the antibiotics as tested in this in vitro system. This may indicate that cysteamine adjunct maintenance therapy may be better at preventing the establishment of BCC colonization in CF than at removing existing biofilms in chronically infected patients; however, the enhancement of antimicrobial activity may prove to be the more

### Table 3: Antimicrobial activities of trimethoprim-sulfamethoxazole and trimethoprim-sulfamethoxazole in combination with cysteamine against Burkholderia isolates versus S/I/R determinations based upon CLSI interpretive criteria

| Organism       | Strain                     | Median MIC$_{100}$ (μg/ml) of: | Trimethoprim-sulfamethoxazole S/I/R | Trimethoprim-sulfamethoxazole (μg/ml) of combination |
|----------------|----------------------------|----------------------------------|-------------------------------------|------------------------------------------------------|
| B. cenocepacia | NCTC 13008                 | 128.00 4/76                      | R                                   | 128/4/76 R                                           |
| B. multivorans | DSMZ 13243                 | 256.00 0.25/4.75                 | S                                   | 256/0.125/2.375 S                                    |
| B. dolosa      | DSMZ 16088                 | 256.00 2/38                      | S                                   | 256/2/38 S                                           |
| B. anthina     | DSMZ 16086                 | 256.00 0.0625/1.875              | S                                   | 256/0.0625/1.1875 S                                  |
| B. ambifaria   | DSMZ 16087                 | 256.00 0.125/2.375               | S                                   | 256/0.125/2.375 S                                    |
| B. stabilis    | NCTC 13011                 | 64.00 4/76                       | R                                   | 64/4/76 R                                            |
| B. cenocepacia | DSMZ 16553                 | >256 4/76                        | R                                   | 128/0.25/4.75 S                                     |
| B. vosmensis   | ATCC BAA-248               | 256.00 0.5/9.5                   | S                                   | 256/0.5/9.5 S                                        |
| B. pyrocinia   | ATCC 15958                 | 256.00 0.25/4.75                 | S                                   | 256/0.25/4.75 S                                     |
| B. vietnamensis | NCTC 10743                | 256 0.5/9.5                     | S                                   | 256/0.5/9.5 S                                        |
| B. multivorans | NCTC 13417                 | 256.00 1/19                      | S                                   | 128/0.125/2.375 R                                   |
| B. stabilis    | NCTC 13417                 | 256.00 2/38                      | S                                   | 256/2/38 S                                           |
| B. cenocepacia | NCTC 13008                 | 256.00 0.03125/0.596875          | S                                   | 64/0.03125/0.596875 S                                |
| B. cenocepacia | 1223                      | 128.00 4/76                      | R                                   | 64/1/19 S                                            |
| B. multivorans | 1225                      | 128.00 2/38                      | S                                   | 64/0.5/9.5 S                                        |
| B. multivorans | 1140                      | 256.00 0.25/4.75                 | S                                   | 256/0.125/2.375 S                                    |
| B. cenocepacia | CFSYN 936                  | 128 2/38                         | S                                   | 64/0.5/9.5 S                                        |
| B. multivorans | CFSYN 1045                 | 256 0.125/2.375                  | S                                   | 64/0.00625/1.1875 S                                  |
| B. cenocepacia | CFSYN 1112                 | 256 4/76                         | R                                   | 128/1/19 S                                           |
| B. cenocepacia | CFSYN 946                  | 64 4/76                          | R                                   | 64/0.25/4.75 S                                      |
| B. multivorans | CFSYN 946                  | >256 2/38                        | S                                   | 256/0.3/9.5 S                                        |
| B. cenocepacia | CFSYN 945                  | >256 0.5/9.5                     | S                                   | 256/0.125/2.375 R                                   |
| B. cenocepacia | NCTC 10743                 | >256 0.5/9.5                     | S                                   | 128/0.5/9.5 S                                        |
| B. multivorans (gen. II) | 05.4136OrgB | >256 4/76                      | R                                   | 256/2/38 S                                           |
| B. cenocepacia (gen. III) | 05.386860OrgB | >256 4/76                      | R                                   | 64/2/38 R                                            |
| B. multivorans (gen. II) | 05.4136OrgA | >256 4/76                      | R                                   | 64/2/38 R                                            |
| B. cenocepacia (gen. IIIA) | 05.66335OrgA | >256 0.125/2.375               | S                                   | 64/0.00625/2.175 S                                  |
| B. stabilis (gen. IV) | 05.51979       | 128 0.5/9.5                     | S                                   | 128/0.5/9.5 S                                        |
| B. vietnamensis (gen. V) | 05.76464OrgC | 256 0.25/4.75                  | S                                   | 64/0.125/2.375 S                                    |

a All results represent the MIC$_{100}$ from triplicate samples from triplicate experiments. All data manipulation was carried out in Microsoft Excel. Resistant or intermediate results are highlighted by shading.
important feature of this compound in this situation. Further research to determine optimum antibiotic combinations and concentrations to eradicate established BCC biofilms may yet prove efficacious.

We purposely did not use an exhaustive panel of BCC strains for this study. We instead employed a focused set of clinically relevant CF isolates from two of the United Kingdom’s specialist CF centers (8 isolates from Glasgow and 16 from Aberdeen) and an additional 12 type strains in order to cover all known BCC genomovars, regardless of clinical relevance.

Cysteamine is in late-stage clinical trials for the treatment of cystic fibrosis and is being developed in oral and inhaled forms for acute exacerbations and chronic longer-term maintenance (10–12). An oral form of cysteamine was investigated in an open-label clinical study (28) in the United Kingdom in which tolerability, absorption, pK, and early evidence of efficacy were assessed in adult CF patients with stable disease. A global two-part registration study for oral cysteamine in acute exacerbations is now being initiated (EudraCT no. 2015-000498-99) for which endpoints will include the reduction in sputum microbial burden over and above that achieved with standard of care therapy (SOCT) exacerbation interventions.

Thus far, cysteamine appears to be a promising candidate treatment for CF, but how its interactions with all components of the complex CF microbiome contribute to its clinical effects is yet to be determined. We have already demonstrated the utility of cysteamine against other, more common CF pathogens that are known to drive acute infectious exacerbations (Pseudomonas in particular) (29, 30). We believe that this study is important in confirming the efficacy of cysteamine against the more insidious BCC and its colonization of the CF airway, which may be eradicated and perhaps prevented by long-term use of an adjunct to SOCT such as cysteamine, which is able to potentiate the effects of existing antibiotics and “switch” BCC to becoming sensitive and also prevent this organism from becoming sensitive and also prevent this organism from

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**TABLE 4** Antimicrobial activities of ceftazidime and ceftazidime in combination with cysteamine against *Burkholderia* isolates

| Organism         | Strain          | Median MIC<sub>100</sub> (µg/ml) of: | Ceftazidime | S/I/R | Ceftazidime | S/I/R | Ceftazidime | S/I/R |
|------------------|-----------------|-------------------------------------|-------------|-------|-------------|-------|-------------|-------|
|                  |                 | Lynoxev alone                      | Ceftazidime alone | S/I/R | combination | (µg/ml) of | alone | combination | (µg/ml) of |
| *B. cenocepacia* | NCTC 13008      | 128.00                              | 2.00         | S     | 128/2       | S     |
| *B. multivorans* | DSMZ 13243      | 128.00                              | 1.00         | S     | 128/1       | S     |
| *B. dolosa*      | DSMZ 16088      | 256.00                              | >16          | R     | 256/>16     | R     |
| *B. anthina*     | DSMZ 16086      | 256.00                              | 1.00         | S     | 256/1       | S     |
| *B. ambifaria*   | DSMZ 16087      | 256.00                              | 1.00         | S     | 256/1       | S     |
| *B. stabilis*    | NCTC 13011      | 128.00                              | 1.00         | S     | 64/0.0625   | S     |
| *B. cenocepacia* | DSMZ 16553      | 256.00                              | 32.00        | R     | 32.00       | R     |
|                  | NCTC 13417      | 256.00                              | >16          | R     | 256/>16     | R     |
| *B. vietnamensis*| ATCC BAA-248     | 256.00                              | 1.00         | S     | 256/1       | S     |
| *B. pyrrocinia*  | ATCC 15958      | 256.00                              | 2.00         | S     | 256/2.00    | S     |
| *B. vietnamensis*| 946             | 64.00                               | 32.00        | R     | 64/32       | R     |
|                  | 888             | 128.00                              | 16.00        | I     | 128/16      | I     |
|                  | 821             | 128.00                              | 1.00         | S     | 256/1       | S     |
| *B. cenocepacia* | 1223            | 256.00                              | 32.00        | R     | 128/8       | S     |
|                  | 1225            | 256.00                              | 2.00         | S     | 128/2       | S     |
|                  | 1237            | >256                                | 16.00        | I     | 256/2       | S     |
| *B. multivorans* | 1140            | >256                                | 16.00        | I     | 256/16      | I     |
|                  | 1142            | >256                                | 2.00         | S     | 256/2       | S     |
|                  | 1247            | >256                                | 16           | I     | >256/>16    | R     |
| *B. cenocepacia* | CSYN 936        | 128                                 | 16           | I     | 128/8       | S     |
|                  | CSYN 1045       | 256                                 | 0.125        | S     | 256/0.125   | S     |
|                  | CSYN 1112       | 128                                 | >32          | R     | 128/>32     | R     |
| *B. cepacia*     | CSYN 946        | 128                                 | 16           | I     | 64/16       | I     |
| *B. multivorans* | CSYN 1081       | >256                                | >32          | R     | >256/>32    | R     |
|                  | CSYN 954        | >256                                | 1           | S     | >256/1      | S     |
|                  | CSYN 945        | >256                                | 2           | S     | >256/2      | S     |
| *B. cepacia*     | NCTC 10743      | 256                                 | 4            | S     | 128/4       | S     |
|                  | NCTC 10744      | >256                                | 2            | S     | >256/2      | S     |
| *B. multivorans* (gen. II) | 05.4136OrgB | 256                                 | 32           | R     | 256/32      | R     |
|                  | 05.3868OrgB     | 256                                 | 2            | S     | 256/2       | S     |
| *B. cenocepacia* (gen. IIIA) | 05.66333OrgA | >256                                | 2           | S     | >256/2      | S     |
|                  | 07.37324OrgA    | >256                                | 8           | S     | >256/8      | S     |
| *B. stabilis* (gen. IV) | 05.51979 | 128                                 | 2            | S     | 128/2       | S     |
|                  | 05.56937OrgA    | 256                                 | 2            | S     | 256/2       | S     |
| *B. vietnamensis* (gen. V) | 05.76464OrgC | 128                                 | 1           | S     | 128/1       | S     |

*All results represent the MIC<sub>100</sub> from triplicate samples from triplicate experiments. S/I/R determination was based upon CLSI interpretive criteria. All data manipulation was carried out in Microsoft Excel. Strains with resistant or intermediate results are highlighted by shading.*

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Fraser-Pitt et al.

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in responses to cysteamine coexposure we have underpinned for BCC (and other organisms in our previous work) are the subject of further study.

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All authors are current or previous employees of NovaBiotics. Deborah O’Neil is a director and shareholder of NovaBiotics Ltd. Derry Mercer and Jennifer Robertson hold share options in NovaBiotics Ltd.

All authors are named inventors on patents (regarding the antimicrobial and dispersant properties of cysteamine) which are wholly owned by NovaBiotics Ltd.

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