The polyamino-isoprenic efflux inhibitor NV716 revives old disused antibiotics against intracellular forms of infection by *Pseudomonas aeruginosa*

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## Introduction & Purpose

WHO considers *P. aeruginosa* (PA) as a priority pathogen for the search of innovative therapies. PA is indeed intrinsically resistant to many antibiotics due to poor outer membrane permeability and/or active efflux [1]. Moreover, it can also adopt specific lifestyles, like intracellular survival, which are poorly responsive to antibiotics [2].

Our aim was to evaluate the capacity of efflux pump inhibitors to restore the activity of old, disused antibiotics, against intracelular PA. We compared PAβN to original polyamino-isoprenic compounds, namely NV731 and NV716 in combination with doxycycline, chloramphenicol (substrates for efflux), and rifampicin (not substrate) [3].

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### MIC of ABs alone or combined with inhibitors against PAO1

<table>
<thead>
<tr>
<th>Experimental condition</th>
<th>DOX</th>
<th>CHL</th>
<th>Rif</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic (AB) alone</td>
<td>8</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AB + NV716 (2.5µM)</td>
<td>1</td>
<td>2</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>AB + NV716 (10µM)</td>
<td>0.5</td>
<td>1</td>
<td>0.125</td>
<td></td>
</tr>
<tr>
<td>AB + NV731 (2.5µM)</td>
<td>4</td>
<td>32</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>AB + NV731 (10µM)</td>
<td>4</td>
<td>16</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>AB + PABN (200µg/mL)</td>
<td>2</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values in bold denote a decrease of ≥ 2 doubling dilutions vs. AB alone*

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### Results

**Main messages**

- NV716 may therefore appear as a useful capacity to impair PA membrane integrity [3].
- NV716 is capable to re-sensitize PA to intracellular persistent forms.
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### References


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### Conclusions

- NV731 had no significant effect on MICs of NV716 (2.5 and 10 µM).
- NV716 (2.5 µM) markedly reduced the MIC of PAβN, 716, 731.
- NV731 and NV716 were able to increase both relative potency (lower C₅₀ value) and maximal efficacy (more negative E₉₀ value) for all drugs.