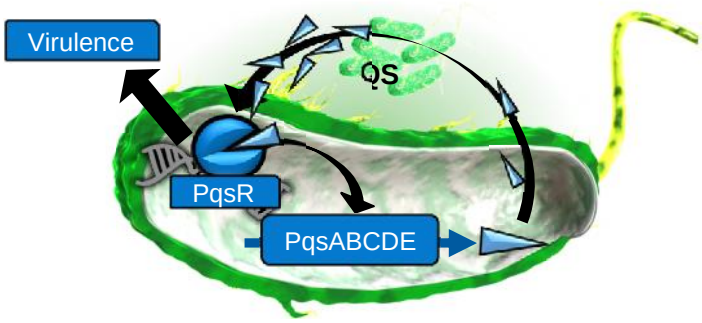

PqsR Inverse Agonists for Adjunctive Treatment of Respiratory Infections by *Pseudomonas aeruginosa* Including NCFB

BioVaria 2019

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Non-Cystic-Fibrosis Bronchiectasis (NCFB): Chronic Infection and Airway Destruction

Dilated bronchi and sputum production predispose to infection by bacteria, including *Pseudomonas aeruginosa* (*PA*)

Diagnosis of *PA* considered major prognostic factor:

- 3-fold increased mortality [1]
- Reduced QoL
- Frequent hospital admissions
- Increased healthcare burden

No registered drugs

Frequent and extended antibioses (systemic & inhaled)

- Early aggressive **eradication therapy** (30-50% success rate [2])
- **Long-term suppressive** antibiotic therapy to reduce bacterial burden and frequency of pulmonary exacerbations [3]

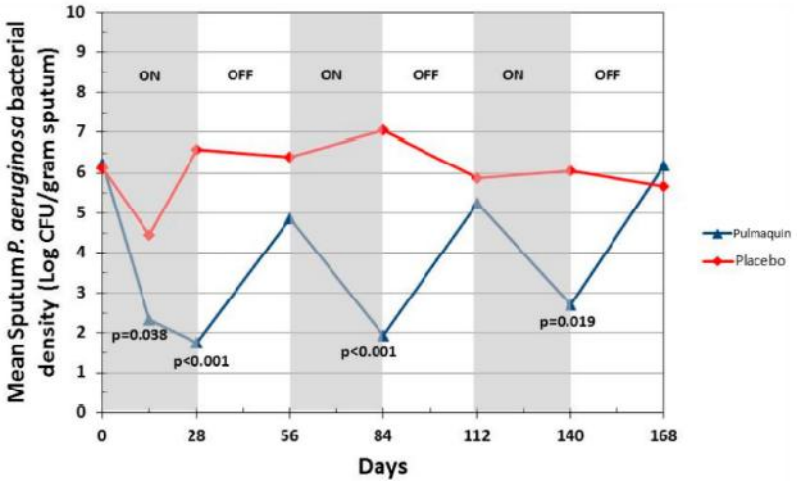
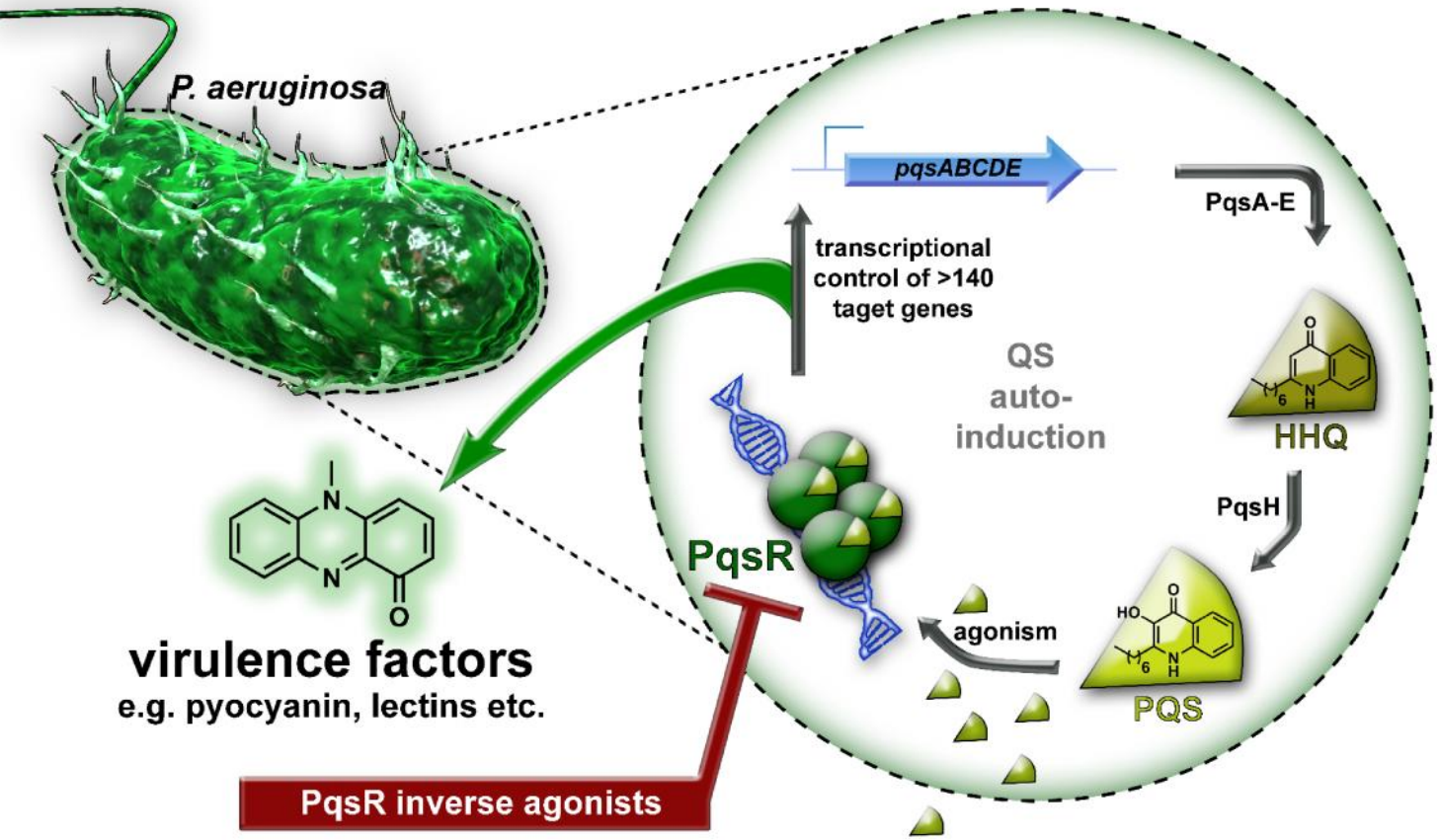


Figure 15. Change in mean sputum PA bacterial density across the 3 treatment cycles (28 days on followed by 28 days off) for Pulmaquin and Placebo groups in the modified intention to treat (mITT) population. Reprinted with permission from [21]. Copyright 2013 BMJ.

[1] Finch et al., Annals ATS, 12(11): 1602-1611 (2015)
[2] Brodt et al., Eur Repir J 44: 382-393 (2014)
[3] Cipolla et al., Pharmaceutics 8:6ff (2016)

Our solution to the problem: Targeting PqsR (MvfR) in virulence



PqsR-dependent regulation:

- Environmental adaptation
- Virulence factor expression
- Iron acquisition
- Redox signalling
- Antibiotic tolerance
- Cytotoxicity
- Immune modulation/evasion

(Lee and Zhang 2015, Lin 2018)

PqsR-independent regulation:
>180 gene products interact with alkylquinolones (e.g. MexG, MtgA, NirS, FleQ, RhlR etc)

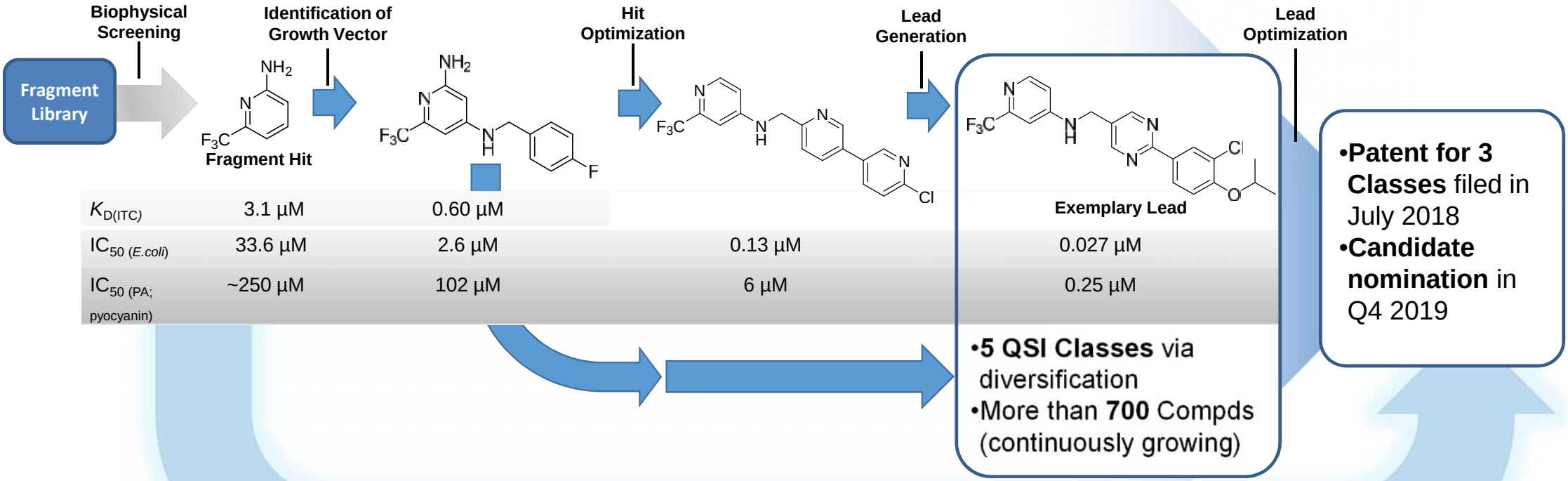
(Rampioni 2016, Hodgkinson 2016, Baker 2017, Dandela 2018)

***pqsR/pqsA* mutant phenotypes: Avirulence**
(Cao 2001, Gallagher, 2002, Lau 2004, Deziel 2005, Xiao 2006, Schertzer 2009, von Bodman 2010)

HIPS-1865 as Adjunctive Treatment of Chronic Respiratory Infections by PA

- **Pathogen-specific**, non-Fleming type PA only agent
  - ➢ **Microbiome sparing**
- Synergistic effect with aminoglycosides through **biofilm activity**
- Opportunity to **enhance compliance** with inhaled aminoglycosides (lowering of dose) and to **improve efficacy** above 30-50% eradication at baseline
  - ➢ Opportunity for combination treatment (Tobi off-patent)
  - ➢ Opportunity for long-term enhanced suppression therapy as well as pre-emptive monotherapy (w/o antibiotic)
- Opportunity for **superiority OLD + NEW vs OLD**, provided treatment effect of NEW is substantial
- Opportunity for application in PA infection in **multiple respiratory conditions** including CF, COPD, Primary Ciliary Dyskinesia

Invention 1/2 – Medicinal Chemistry-driven QSI Discovery



	Fragment Hit			Exemplary Lead
$K_{D(ITC)}$	3.1 µM	0.60 µM		
$IC_{50\ (E.coli)}$	33.6 µM	2.6 µM	0.13 µM	0.027 µM
$IC_{50\ (PA;\ pyocyanin)}$	~250 µM	102 µM	6 µM	0.25 µM

- **5 QSI Classes** via diversification
- More than **700** Compds (continuously growing)

- **Patent for 3 Classes** filed in July 2018
- **Candidate nomination** in Q4 2019

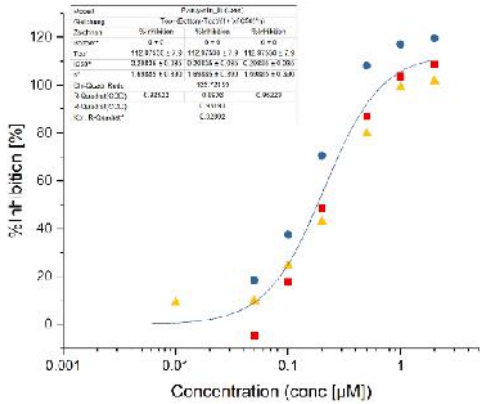
Fragment-based Drug Discovery guided by **stringent TLP/TCP**

QSI, quorum sensing inhibitor
TLP, Target Lead Profile
TCP, Target Candidate Profile

A. S. A. Ahmed, M. Empting , M. Hamed, R. W. Hartmann, J. Haupenthal, T. Hesterkamp, A. A. M. Kamal, C. K. Maurer, T. Röhrig, C. Schütz, S. Yahiaoui, M. Zender, PqsR Inverse Agonists 2018 Ref. No: EP18181475

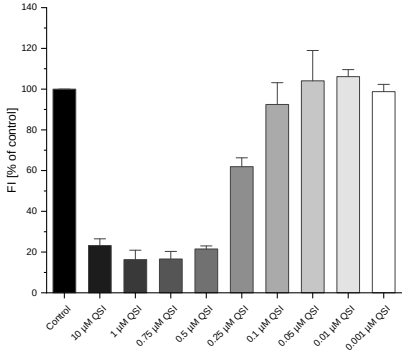
Invention 2/2 – Optimized Features

Potent antivirulence efficacy



Abolishes pyocyanin & autoinducers

➢ Disrupted virulence and signalling



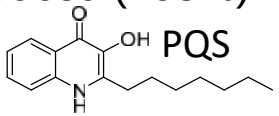
Disintegrates biofilm & reduces eDNA

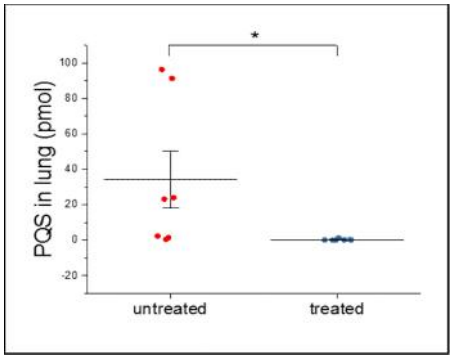
➢ Reduces biophysical barrier to antibiosis

In vivo target engagement

- 5x10^7 cfu/lung inoculum NH57388A mucoid isolate
- Treatment 3x5 mg/kg Lung preparation after 3d

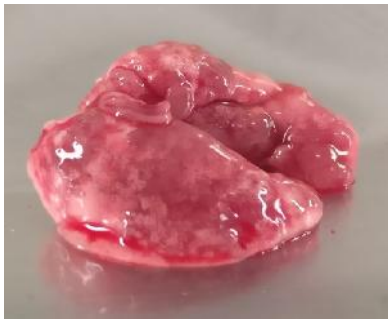
➢ All autoinducer levels reduced (>95%)



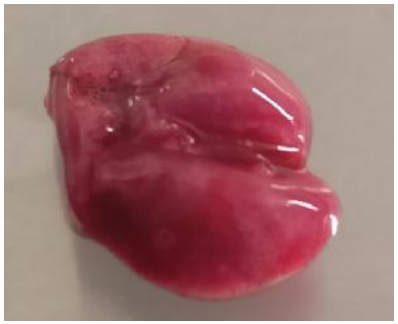


➢ Reduced lesions in treated lungs

➢ CFU reduced 2-fold



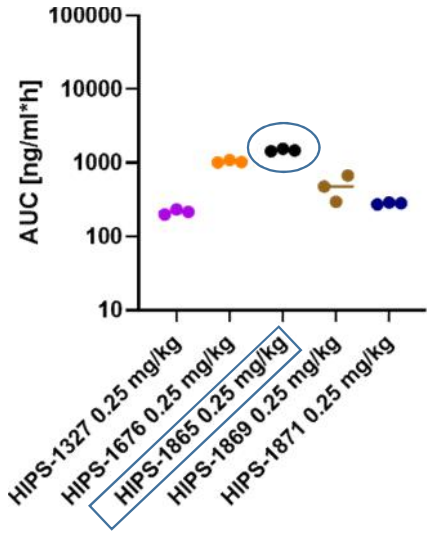
untreated



treated

Favourable PK

- Optimized for lung retention after local application (inhalation/instillation)
- PK parameter: AUC in bronchoalveolar lavage fluid (BALF)



➢ Ideal for co-administration with inhaled antibiotics (e.g. Tobramycin)

$150M Annual Market Potential for NCFB

[1] Weycker et al., *Chron. Resp. Dis. 14(4), 377-384* (2018)
[2] Finch et al., Annals ATS, 12(11): 1602-1611 (2015)
[3] Blanchette et al., *Med Sci* (2017) doi:10.3390
[4] de la Rosa Carrillo et al., *Respiration* 11: 1-11 (2018)
[5] https://www.idstewardship.com/comparison-avycaz-vabomere-zerbaxa/

Potential number of patients addressable with this innovative treatment option

- Ca. 140,000 patients per year in the major pharmaceutical markets [1,2]

Treatment and cost assumptions

- $ 7.000 per patient per year [5]
- 15% market penetration

Current attributable treatment cost

- Ca. ~$30,000 per patient per year
- Number and cost of hospital admissions per year as major cost driver [3;4]

Taken from [1]

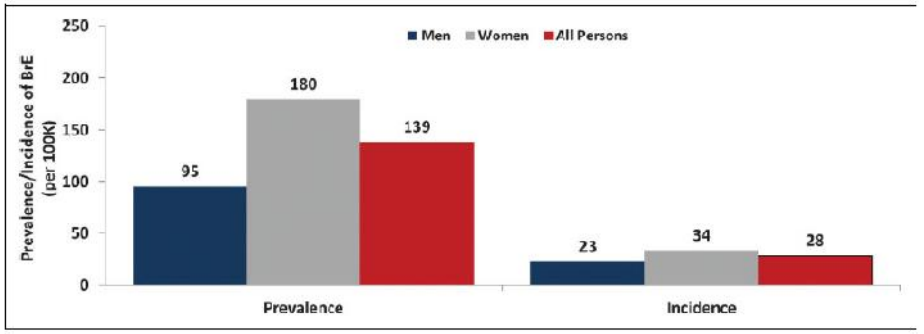


Figure 1. Prevalence and incidence (annual) of bronchiectasis among US adults, overall and by sex.

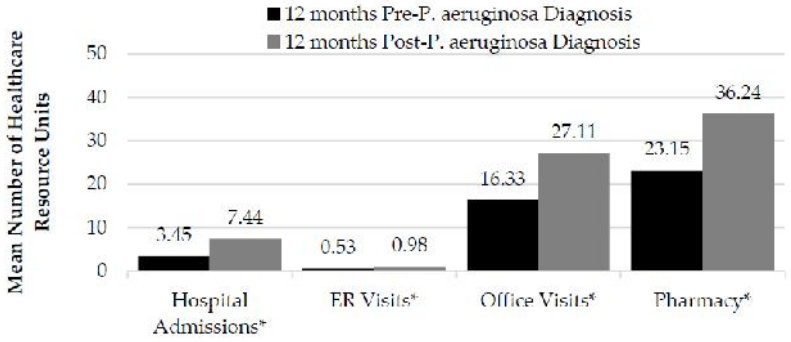
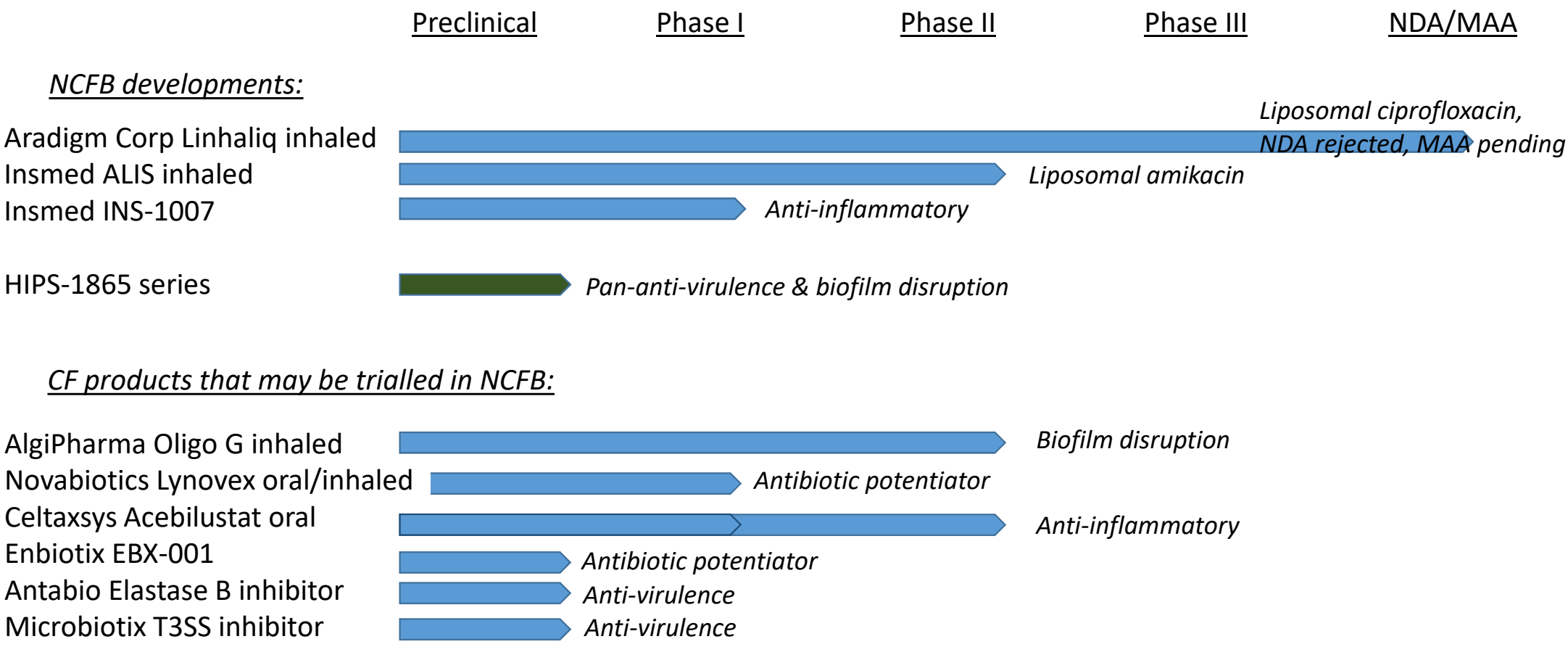


Figure 2. Healthcare utilization (pre- vs. post-*P. Aeruginosa*; * $p < 0.0001$).

Taken from [3]

Active Space, but no Advanced Head-to-head Competition



Intellectual Property

IP owned by HZI

- **Patent family based on Intellectual Property WO2015149821**
  - Priority application with the title “PqsR Modulators” filed 2014, European Patent granted (EP3126333 B1), US patent application pending
  - Claims cover first hit series

- **Patent family based on EP18181475**
  - Priority application with the title “PqsR Inverse Agonists“ filed on July 3, 2018
  - Claims cover current lead series
  - International follow-up application will be filed in July 2019 claiming priority of EP18181475 covering further modified structures due to new growth vector

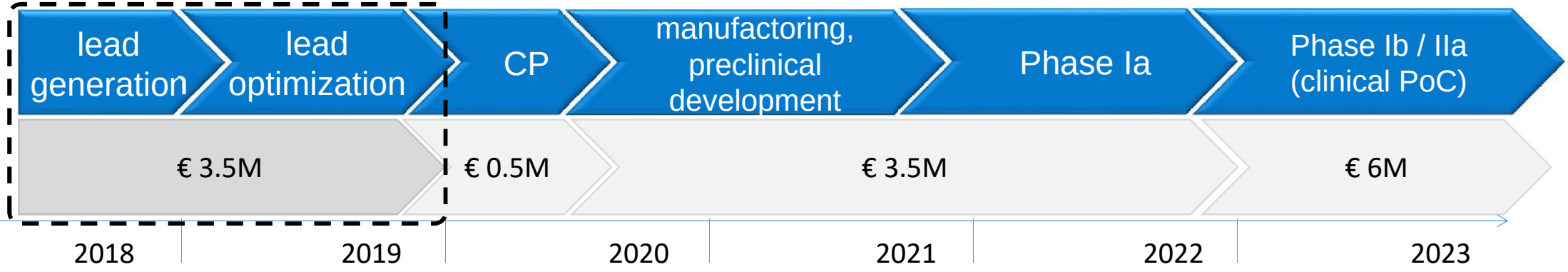
IP landscape

- **So far no patents identified limiting our activities**

Risks and Bottlenecks

- Lack of precedence in clinical development
- Complexicity in view of tractable animal models; lack of established PK/PD indices
- Opportunity and technical challenge of the respiratory route
- As pathogen-specific agent regular diagnosis of pathogen is mandatory
- Improved standard-of-care (e.g. approval of inhaled amikacin)

Development Status and Resources Needed



Funding (~3.5 M €):
- Helmholtz validation fund
- DZIF Flexible Funds
- HZI's innovations fund Pre-4D

Candidate nomination

- Project in lead optimization stage driven by a stringent target candidate profile (TCP)
  - efficacy in complex assays (biofilm, AQs, *in vivo*…)
  - pulmonary retention (lung PK)
  - clean safety pharmacology profile
- 2 murine lung infection models for *in vivo* target engagement & efficacy in combination with antibiotics

We are looking for

- Partners to co-develop product (i.p. experience with and technologies in respiratory route)
- Licensing partners
- VC/CVC partners who want to be updated on project as we progress

We see opportunities for

- Continued non-dilutive funding up to and including phase I

Meet us at Poster D1

TT Contact:

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