Project title: A dual-action drug approach toward improved treatment of chronic *P. aeruginosa* biofilm infections

Mentor 1: Claus Moser, medical doctor, PhD. Department of Clinical Microbiology, Rigshospitalet. External associate professor at Institute for Immunology and Microbiology (ISIM), UCPH (moser@dadlnet.dk)

Mentor 2: Henrik Franzyk, Assoc. Prof., PhD. Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, UCPH (henrik.franzyk@sund.ku.dk)

Framework: Outline of overall framework of the translational environment offered by the mentors:

Henrik Franzyk (HF) has been involved in several projects on discovery of peptide-based antibacterial hits that were developed into potential leads. Facilities dedicated to preparation of building blocks, solid-phase synthesis, purification and analysis are available in the laboratories of HF. Also, HF has extensive experience with interdisciplinary projects comprising initial drug design, synthesis, formulation and *in vitro* testing, which enables a broad-spectrum mentorship in early-phase translation.

Claus Moser (CM) has focused on microbial diagnosis and treatment of infectious diseases. CM has been involved in several pre-clinical and clinical projects. Emphasis has been on biofilm infections from basic science and relevant *in vivo* models to clinical research. The CM group has interest in understanding pathophysiology of infections and improving outcome, e.g. by potentiating antibiotic therapy. Several model systems for efficacy testing of new drugs are available in the group.

Project synopsis: Theme to be developed into a specific research project:

Most chronic bacterial infections involve formation of biofilms that are particularly tolerant to antibiotics and rapidly develop resistance. Examples comprise catheter-associated urinary tract infections, chronic pulmonary infections in cystic fibrosis patients, and chronic wounds that all involve *P. aeruginosa* biofilms. This increasing healthcare problem results in high societal costs and reduced patient welfare.

Dual-action antibiotics display activity via an ability to interact with two different
targets. Such agents may be constructed by chemical linkage (temporary or permanent) of two antibiotics or fragments thereof.

The aims of the proposal comprise: (i) further development of a model system for susceptibility testing of biofilms to novel antibiotics, enabling: (ii) identification of potential dual-action antibiotics from synthetic compound arrays, that undergo: (iii) comparison with simple combination therapy on clinical isolates, and (iv) final testing in animal models.

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<th>Profile of potential fellow</th>
<th>Desired background and scientific qualifications of fellow/mentee:</th>
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<td>▪ PhD degree in chemistry (organic, bioorganic or medicinal), pharmaceutical sciences, microbiology or chemical engineering (including microbiology-oriented or other relevant specialization)</td>
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<td>▪ Strong motivation and excellent scientific/technical skills</td>
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<td>▪ Abilities to publish results and translate these into medical applications</td>
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<td>▪ Attraction to interdisciplinary research</td>
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<td>▪ Ambition to pursue further education</td>
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<td>Name</td>
<td>Claus Moser</td>
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<tr>
<td>Title</td>
<td>Medical doctor, PhD</td>
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<tr>
<td>Current department(s)</td>
<td>Department of Clinical Microbiology (DCM), Rigshospitalet (RH). Institute for Immunology and Microbiology (ISIM), Copenhagen University.</td>
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<td>Current position(s)</td>
<td>Afdelingslæge (Consultant), and external associate professor</td>
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| Education/training | 2005 Specialized in Clinical Microbiology  
1999 Ph.D, University of Copenhagen  
1993 Medical exam, University of Copenhagen |
| Scientific career profile | Contributions to basic, clinical and translational science: Contributed to in vitro biofilms models, and antibiotic biofilm pharmacokinetic. I have performed studies on the host response towards biofilm infections, and have developed relevant animal models of biofilm infections. These studies are hypothesis-driven based on clinical observations directed toward clinical use (i.e., translational science). Contributed to clinical studies on microbial diagnosis, host responses and treatments.  
Research group: Constituted of former and present PhD students, as well as 3 young doctors preparing PhD studies. In addition, one experienced technician.  
Scientific environment: I am financed by The Novo Nordisk "Borregaard Clinical Scientist Fellowship" grant. We have access to clinical and research facilities at our DCM, at ISIM, and the animal facilities.  
Selected Current collaborators: N. Høiby (Consultant, Prof. DCM, RH), H. Bundgaard (Consultant, Prof. Cardiology dept., RH), Ole Hyldegaard (Consultant, Center of Head- and Orthopedics, Hyperbaric Medicine, RH), T. Pressler (Consultant, CF Center, RH). |
| Bibliometric summary | 114 peer-reviewed articles and reviews (and 24 other publications). For peer-reviewed publications: 13 first, 19 second, and 20 last authorshipa; 4.196 citations (WoS); h-index 31 (WoS).  
List of 10 most significant publications:  


Contributions to mentoring, training, supervision

**Mentoring philosophy:** Mentoring is a highly responsible position, with individual tasks depending on the mentored person. Best performed with frequent contact.

**Supervision experience:** One PhD student currently being supervised, one PhD student applying for money, two more on their way. Nine former PhD students who have specialized (n=2)/are specializing (n=3) as medical doctors. One associate professor and one post doc ISIM, two are employed in private companies.

**Teaching:** Several years of teaching medical students. I teach specializing medical doctors, teach at PhD courses and international workshops.
### Name
Henrik Franzyk

### Title
Associate Professor, PhD

### Current department(s)
Department of Drug Design and Pharmacology

### Current position(s)
Associate Professor

### Education/training
- 4-11-1993 PhD (Natural Products Chemistry), Technical University of Denmark
- 31-1-1991 MSc Engineering (Chemistry), Technical University of Denmark

### Scientific career profile
*Scientific and technical expertise:* Design, synthesis and optimization of biologically active compounds: (i) Structure-activity studies of antibacterials and potentiators of antibiotics; (ii) Bacterial delivery of antisense antibiotics; (iii) Mechanisms and structural optimization of immunomodulating compounds; (iv) Studies towards improved macromolecular drug delivery; (v) Design and synthesis of unnatural amino acid and peptidomimetic building blocks.

*Research group:* 3 postdocs, 2 PhD students, 2 lab technicians (of which one is part time allocated staff and one is full-time externally funded), 2 MSc Pharm students.

*Scientific environment:* The group is the medicinal chemistry partner in CEPAN (Center for Peptide-based Antibiotics) funded via a Challenge grant from the Novo Nordisk Foundation (share: 14.9 mio. DKK; project period: 2017-2023).

*Selected current collaborators:* C. Dahlgren (Prof., University of Gothenburg); I. Mellor (Assoc. Prof., University of Nottingham); J. Kelly (Prof., London School of Hygiene & Tropical Medicine), N. Høiby (Prof., Rigshospitalet), P. E. Nielsen (Prof., ICMM, KU-SUND; Leader of CEPAN), L. Guardabassi (Ross University/KU-SUND), H. M. Nielsen (Prof., Dept. Pharmacy, KU-SUND), C. Foged (Prof., Dept. Pharmacy, KU-SUND), B. Brodin (Prof., Dept. Pharmacy, KU-SUND).

### Bibliometric summary
127 peer-reviewed articles and reviews (and 71 other publications). For peer-reviewed publications: 18 first, 22 second, and 33 last authorships; 2.126 citations (WoS); h-index 26 (WoS); average Impact factor: 3.72.

*List of 10 most significant publications* (* denotes corresponding author(s)):
- 76. Jahnsen, R. D.; Haney, E. F.; Franzyk, H.*; Hancock, R. E. W.* Characterization
of a proteolytically stable multifunctional host defense peptidomimetic. Chem Biol 2013, 20, 1286-1295. (IF 5.92)

**Contributions to mentoring, training, supervision**

**Mentoring philosophy:** The mentee will always be encouraged to carefully search the literature to establish a solid basis for designing experiments to prove hypotheses. Meanwhile, I will convey that it is mandatory to critically assess validity of earlier findings (due to an increasing amount of research deficient in proper evaluation). Moreover, the latter also applies to own preliminary results.

**Supervision experience:** Previously: supervision of 7 PhD students and 3 postdocs; co-supervision of 13 PhDs and 4 postdocs. Currently: main supervisor for 2 PhD students and 3 postdocs; co-supervisor for 4 PhDs and 1 postdoc. Two of these have progressed into research top management positions, while most hold positions in research and development (e.g., at Novo Nordisk or Leo Pharma).

**Teaching:** Course director for ‘Biopharmaceuticals: Bioorganic Chemistry’ (lectures, class sessions and laboratory instruction/supervision) on MSc level.