AMR
ANTIMICROBIAL
RESISTANCE
Interdisciplinary
Research Group

# Research Projects in the SMART AMR IRG

(October 1, 2019)

## 1. Project Title: Rapid and Sensitive Bacteria Separation/Concentration from Blood with a Functionalized Filter

**MIT Faculty Advisor**: Jongyoon HAN
**Mentor**: Yaoping LIU
**Email Address**: liu.yaoping@smart.mit.edu

**Project Description**

Bloodstream infections continue to be a major public health problem worldwide, associated with high morbidity and mortality. Sepsis from bloodstream infection annually affects over 20 million people worldwide, with a mortality rate of 30–40%. Treatment within six hours after the first symptoms of bacteremia is crucial otherwise the infection may progress to severe sepsis. The initial treatment with broad-spectrum antibiotics is not only inadequate but also encourages antibiotic resistance. It is widely recognized that early detection, accurate species identification, and verification of antibiotics susceptibility is a requisite for rapid diagnosis and optimally targeted antimicrobial treatment.

However, the clinical routine bacterial blood cultures associated with antibiotics susceptibility testing (AST) require a long time-to-result (>72 hours), and suffer from low sensitivity. Worse still, approximately a third of patients with severe sepsis never have positive blood cultures.

Recent diagnostic strategies including polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA), and mass spectrometry often fail due to the low-abundance (<100 CFU/mL) of bacteria and the interference from a high background blood cellular components, if without culture-based enrichment. To date there are no FDA approved diagnostics for direct detection of bacteria in whole blood without culture-based enrichment. More recent micro/nano technologies show promises with improved detection sensitivity, while still require the sample processing, especially bacteria separation from clinical sample matrix as an initial step.

In short, **a rapid and sensitive separation/concentration of low-abundance bacteria from blood** counts for much in advanced molecular diagnosis (detection and identification) and antibiotics susceptibility testing to promote the personalized therapy and improve the prognosis.

**Goals**

The purpose of this project is to establish a rapid and sensitive bacteria separation/concentration from blood samples based on a previously developed high-performance filter (more details in ref. 1-3). An adhesion-mediated capture of bacteria during filtration will be studied, including electrostatic force attraction and topomorphological match, in the aspects of experimental investigation and theoretical mechanism exploration.

**In the experimental parts, there would contain several types of surface modifications of filter for different purposes:**

1) **Positively-charged modification for efficient bacteria (with a negatively-charged wall) capture during filtration**
2) **Nanostructure (high surface-to-volume ratio) functionalization for topological match based bacteria capture**
3) **Biocompatible sacrificial layer coating for controllable release of bacteria after filtration for downstream analysis (ID, AST, *etc.*)**

The above mentioned functional modifications on the high-performance filter are expected to produce a novel strategy for rapid and sensitive bacteria. With the functionalized modification of the filter, a rapid (<30 min) and sensitive (<100 CFU/mL) bacteria separation from blood samples (3-5 mL) would be established. Meanwhile, the separated bacteria will be concentrated into a small volume with release from filter for downstream analysis. The downstream analysis will be performed in various platforms together with the collaborators, including MRR rapid testing (see ref.4), digital PCR for ID/AST, etc.

**Prerequisites/Skills**

1) Paper searching and reviewing for specific information extraction and summary
2) Coordination and organization in team work
3) Punctuality is necessary
4) Biochemical profession in surface modification is preferable
5) Knowledge and experience in image processing is a plus

**Types of Software Applications**

Image J, Matlab, or similar basic imaging processing to count bacteria on the filter

**Individual or Team Project**

Individual and teams are both acceptable

**Relevant Papers and or URLs**

1) Y. Liu, T. Li, M. Xu, *et al*., A high-throughput liquid biopsy for rapid rare cell separation from large-volume samples, Lab on a Chip, 19, 68 (2019), Back cover.

2) W. Zhou, Y. Liu, M. Ran, *et al*., Rapid liquid biopsy for Mohs surgery: rare target cell separation from surgical margin lavage fluid with a high recovery rate and selectivity, Lab on a Chip, 19, 974 (2019), Back cover.
3) Y. Liu, H. Xu, W. Dai, *et al*., 2.5-dimensional Parylene C micropore array with large area and high porosity for high-throughput particle and cell separations, Microsystems & Nanoengineering, 4, 13 (2018).
4) S. T. Surendran, A. Xiong, P. Lin, *et al*., "Enhancing the sensitivity of micro magnetic resonance relaxometry detection of low parasitemia Plasmodium falciparum in human blood", Scientific Reports, 9, 255 (2019).
5) http://www.rle.mit.edu/micronano/filtration/
6) https://amr.smart.mit.edu/staff-and-students/dr-yaoping-liu

## 2. Project Title: Theoretical Mechanism Study in Filtration Based Bacteria Separation

**MIT Faculty Advisor**: Jongyoon HAN
**Mentor**: Yaoping LIU
**Email Address**: liu.yaoping@smart.mit.edu

**Project Description**

Bloodstream infections continue to be a major public health problem worldwide, associated with high morbidity and mortality. Sepsis from bloodstream infection annually affects over 20 million people worldwide, with a mortality rate of 30−40%. Treatment within six hours after the first symptoms of bacteremia is crucial otherwise the infection may progress to severe sepsis. It is widely recognized that early detection, accurate species identification, and verification of antibiotics susceptibility is a requisite for rapid diagnosis and optimally targeted antimicrobial treatment. And all the aforementioned diagnostics require bacteria separation and concentration from a high background blood cellular component as an initial step.

There have been lots of technologies developed for bacteria separation from blood. Among them, filtration based technologies is advantageous in achieving a rapid (high volume throughput) operation and totally physical based separation (avoiding biochemical interference for downstream analysis). For the separation mechanism in filtration, besides size differences, there also exits surface adhesion.

**In this project, the theoretical mechanism behind surface adhesion in filtration will be studied, and finally provides guidance in filtration device designs and sample pre-treatment.**

**Goals**

The purpose of this project is to establish a theoretical model to describe the surface adhesion of bacteria to the filter surfaces with different properties (electrostatic charge, topological structures). There are some related references, and the main aspects in this project will mainly contain but not limited to the following:

1) **Surface charge induced electrostatic force**
2) **Topological match based arrangement and bacteria surrounding behavior**
3) **Flow velocity influenced contact probability**

Besides the theoretical modeling exploration, there will also have experimental results to verify for model optimization. After theoretical model construction, a guidance for filtration device design and fabrication, and sample pretreatment and filtration operation condition (flow rate) will be realized, which will be universally applicable for various bacteria separation from different body fluids.

**Prerequisites/Skills**

1) Paper searching and reviewing for specific information extraction and summary
2) Coordination and organization in team work
3) Punctuality is necessary
4) Good foundation in physics
5) Basic programming (e.g. Matlab, C language)

**Types of Software Applications**

Matlab, C Language, or simple programming

**Individual or Team Project**

Individual and teams are both acceptable

**Relevant Papers and or URLs**

1) W. G. Pitt, M. Alizadeh, G. A. husseini, *et al*., Rapid separation of bacteria from blood—review and outlook, Biotechnol. Prog., 32, 823 (2016).
2) F. J. H. Hol and C. Dekker, Zooming in to see the bigger picture: Microfluidic and nanofabrication tools to study bacteria, Science, 346, 438 (2014).
3) F. Wu and C. Dekker, Nanofabricated structures and microfluidic devices for bacteria-from techniques to biology, Chemical Society Review, 45, 268 (2016).
4) A. I. Hochbaum and J. Aizenberg, Bacteria pattern spontaneously on periodic nanostructure arrays, Nano Letters, 10, 3717 (2010).
5) http://www.rle.mit.edu/micronano/filtration/
6) https://amr.smart.mit.edu/staff-and-students/dr-yaoping-liu

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## 3. Project Title: Nanoparticles Therapeutics for the Treatment of Bacterial Infections

**MIT Faculty Advisor**: Paula HAMMOND
**Mentor**: Federica ARMAS
**Email Address**: armas@smart.mit.edu

**Project Description**
Antimicrobial resistance (AMR) occurs when bacteria or other microorganisms are able to resist antibiotics or other medications that would usually be effective in killing the microbe. Resistance can be conferred by genetic elements or by phenotypic traits. A major phenotypic attribute that limits the efficacy of many therapeutics is the ability of bacteria to form biofilms. Biofilms are multicellular communities kept together in an extracellular matrix that they produce, which presents a diffusion barrier to drugs. It has been estimated that 65% of microbial infections are associated with biofilms, and biofilm cells are 100 to 1,000 times more resistant to antimicrobial agents than planktonic bacterial cells.

In our lab, we are developing novel nanoparticle therapeutics loaded with water-soluble and -insoluble drugs. The goal of our research is to create more powerful weapons to combat otherwise resistant bacterial infections and to limit the host toxicity of drugs by controlling their delivery. Specifically, this project is focused on the development of drug-loaded nanoparticles able to penetrate and transport drugs inside bacterial biofilms.

**Goals**
The goals of this project are to determine the *in vitro* sensitivity of bacteria towards various antibiotics, antimicrobial agents and drug-loaded nanoparticle formulations. Susceptibility assays will be used to understand the effectiveness of new therapies compared with existing ones. Nanoparticles will be generated, loaded with various drugs, and their efficacy will be tested against bacterial strains outlined in the WHO list of antibiotic-resistant "priority pathogens".

Students will be able to:
1) Design and perform susceptibility assays
2) Work in aseptic conditions
3) Acquire the ability to test drugs against bacteria
4) Gain exposure to nanoparticle formulation

**Prerequisites/Skills**
Students should understand the basic principles of microbiology. Basic biological laboratory skills are preferred but not required.

**Types of Software Applications**
Not identified

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**Individual or Team Project**
Individual or pairs are encouraged to apply

**Relevant Papers and or URLs**
Further details regarding the AMR IRG and Hammond Group projects can be found at www.amr.smart.mit.edu.