# Bridging medicine and biomedical technology: enhance translation of fundamental research to patient care 

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#### Abstract

The 'Bridging medicine and biomedical technology' special all-congress session took place for the first time at the OSA Biophotonics Congress: Optics in Life Sciences in 2017 (http://www.osa.org/enus/meetings/osa_meetings/optics_in_the_life_sciences/bridging_medic ine_and_biomedical_technology_specia/). The purpose was to identify key challenges the biomedical scientists in academia have to overcome to translate their discoveries into clinical practice through robust collaborations with industry and discuss best practices to facilitate and accelerate the process. Our paper is intended to complement the session by providing a deeper insight into the concept behind the structure and the content we developed.


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OCIS codes: (170.0170) Medical optics and biotechnology; (170.1870) Dermatology; (170.4470) Ophthalmology; (custom) Translational research.

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## Introduction

Translational research has evolved over the last decade into a new science encompassing many scientific and engineering disciplines, medicine, team science, project management and partnership development with industry [1,2]. Its promise is the ability to carry the benefits of new discoveries across fundamental research, proof-of-concept and development stages to accelerate transfer of novel and affordable diagnostics and therapeutics to patient care. Success is determined by two factors: (i) relevant and well-defined practical problems to be solved; and (ii) the engagement, at appropriate stages, of clinicians, scientists and engineers in academia with industry.

The field of biomedical optics and biophotonics has a highly successful forty year track record of performing original and translational research that led to laser surgery, lightactivated therapies, optical diagnostics and imaging and the emergence of new light-based technologies that can sense, monitor and manipulate biological processes in the human body [3,4]. Novel models to facilitate and accelerate the translation process, creative mechanisms to support problem-driven research work, innovative education and training programs have been initiated and pioneered in this field $[1,3,5,6]$.

## The concept

Despite growing awareness of the significance of translational research and the progress that has been made to support it, many challenges remain. Academia and industry are both essential in fulfilling the mission of promoting new diagnostics and treatments to alleviate burden of human disease. In our experience, one major factor that could enhance the ability of academia to bridge with industry and engage in productive partnerships is a more complete definition of the problem to be solved at a project's conception. Key questions need to be asked in order to address this limitation. How and at what stage of their research do scientists and engineers engage the dialogue with clinicians? How do clinicians identify and assess technologies that can solve their problems? And, how do clinicians, scientists and engineers together define a relevant solution, design and perform the proper proof-of-concept experiments and then engage with industry technology development partners?

At the Wellman Center for Photomedicine (WCP), one of the five thematic research centers at Massachusetts General Research Institute, we have a long tradition of encouraging and supporting translational research stemming from a culture that embraces the potential of light and optical techniques to impact human health [3].

One model to bridge academia with industry that we pilot at the WCP is targeting the early stage translation of a new idea from fundamental research to proof-of-concept. Figure 1 illustrates the problem-driven research planning phase. The goal is to have the project clinical lead and scientific/engineering lead take a systematic approach together to understand the
practical problem to be solved, formulate the required clinical specifications and identify possible solutions and technologies to be tested. By working in concert from the beginning through intensive and synergistic interaction, various innovative technologies can be developed and applied to solve the specific clinical problem. Figure 2 depicts the working flow in the first phase of research planning followed by the second phase including manufacturing of the prototype and performance of the proof of concept experiments. The outcome of this second phase is critical for a successful transition to the development stage of translation, therefore our objective is to engage with industry partners for both prototype manufacturing and proof of concept experimental work.


Fig. 1. Problem-driven research planning.


Fig. 2. Early stage translation working flow from problem-driven research planning to application relevant proof-of-concept experiments conception and performance.

## Examples

To illustrate the concept, we selected two concrete examples of important clinical problems in dermatology and ophthalmology that we are trying to solve.

## Dermatology

## Problem

Cellulitis is a bacterial infection of the skin that presents with expanding redness, swelling, pain, and warmth. Cellulitis affects 14.5 million Americans annually at a cost of $\$ 3.7$ billion dollars $[7,8]$. Unfortunately, over $30 \%$ of patients with 'cellulitis' are actually misdiagnosed [9]. These patients are unnecessarily admitted to the hospital, inappropriately treated with
antibiotics and subsequently at risk for antibiotic-related complications such as anaphylaxis or Clostridium dificile infection [9].

Currently, there are no objective diagnostics for cellulitis [10]. Standard blood lab tests are neither sensitive nor specific. Bacterial cultures using standard microbiology methods, from either skin and blood, are rarely positive and take $24-48$ hours for results. As such, clinicians typically make the diagnosis of cellulitis based on history and physical exam alone. However, given the many skin conditions that mimic cellulitis (collectively known as 'pseudocellulitis'), history and physical exam frequently leads to misdiagnosis. Therefore, novel objective diagnostics for differentiating cellulitis from pseudocellulitis are needed to improve patient care and reduce unnecessary healthcare costs.

## Specs

Any potential novel diagnostic for cellulitis must meet various internal and external constraints. The 'default' for clinicians when they see spreading redness, swelling, pain, and warmth of the skin is to diagnose cellulitis. This ensures they treat all patients with cellulitis (high sensitivity), however they over treat at least $30 \%$ (low specificity). Therefore, accuracy is a priority, requiring high sensitivity to catch all patients with cellulitis but also high specificity to prevent misdiagnosis. Further, the diagnostic needs to provide an 'answer' rapidly, ideally within 1-2 hours or less of patient presentation to the Emergency Department (ED). This timing fits within the flow of a busy ED, allowing them to discharge patients and clear valuable beds. In that regard, the diagnostic must be point-of-care to allow treating providers to triage their patients and make the decision whether to provide antibiotics or not. The tool should be easy to use, requiring only minimal training, thereby maximizing adoption and use across physicians and physician-extenders (i.e. nurses, medical assistants, etc.). Finally, a new diagnostic should be relatively low cost.

## Solutions

Dermatologists rely extensively on their visual diagnostic acumen; however, this does not scale well given the limited number of providers. In regard to the problem of cellulitis misdiagnosis, we want to investigate various non-invasive optical modalities to assess skin hemodynamic and metabolic parameters. To accomplish this, we need expertise in biophotonics, thermal heat transfer, data processing, machine learning, and mathematical modeling. This requires establishing collaborations with biomechanical engineers, electrical engineers, computer engineers, and biostatisticians. Recently we have developed a predictive model using skin thermal imaging [11]. Utilizing the temperature difference between the affected area and unaffected area of skin in patients with presumed cellulitis at the time of emergency room presentation, we demonstrate an accuracy of $87.5 \%$ in a validation cohort. We are currently exploring several additional optical modalities to further enhance the accuracy of our thermal imaging model. We anticipate that these diagnostic tools will provide valuable data points not available through visual exam alone. Our prototypes and models are currently being validated in larger clinical proof of concept studies.

## Ophthalmology

## Problem

In ophthalmology, the development of short-sightedness (myopia) is an increasingly common problem with more than 2.5 billion estimated to be affected worldwide by 2020 [12]. Myopia is a pathologic and irreversible elongation of the eye. Studies in Asian college students found a prevalence of $95 \%$ for myopia and $25 \%$ for high myopia (the most severe form) [13]. Unfortunately, high myopic patients are severely affected by this elongation of the eye with a 60 -fold increased risk for developing a retinal detachment or other late-onset consequence compared to normal eyes [14]. Treatment for myopia includes optical aids, such as glasses or
contact lenses, and LASIK or other refractive procedures [15]. However, these strategies only treat the symptoms and not the cause of the disease. Neither the underlying pathologic mechanism of axial elongation [16] nor the long-term consequences that accompany it are addressed by current solutions. Prior surgical approaches to halt the axial growth, like posterior scleral reinforcement, have failed [17] and a pharmaceutical approach using topical application of atropine to break the feedback mechanism of axial elongation demonstrated only limited clinical success [18].

## Specs

One promising approach to prevent the axial elongation process is scleral crosslinking, in which the sclera (surrounding tissue of the eye globe) is artificially stiffened in order to prevent axial growth [19]. The increase in stiffness is achieved by a light activated dye, which generates radicals and subsequently induces new covalent bonds within and between collagen molecules [20]. While we recognized the potential benefits of scleral crosslinking, the major barrier in previous studies was the invasive method required to guide light onto the dyesoaked sclera due to the eye's location inside the orbit. Before brainstorming possible solutions to this problem, we determined that the clinical requirements of any suitable solution must include a homogeneous irradiation profile directed only towards sclera, the ability to use different wavelengths and irradiances, thin dimensions, minimal heat development and biocompatibility.

## Solutions

Utilizing the clinical input, a team of scientists and engineers in biophysics, photochemistry, and biomedical engineering investigated potential approaches and developed feasible prototypes for clinical use in humans. A promising result came with the development of flexible waveguides in which light was coupled by means of a fiber and then homogeneously transmitted onto the sclera. First, prototypes were built and basic experiments were conducted [21], and currently an in vivo rabbit proof of concept study investigating the feasibility and efficacy of the light delivery system is underway at WCP. Further, during profound discussions, the idea came up of how to identify possible patients which are in need of this artificial stiffening. This resulted in our next project to develop a diagnostic device for myopia, which is under investigation at the moment at WCP.

## Conclusion and perspective

These two examples illustrate the emergence of clinically initiated research projects. In both cases, important problems have been identified by clinicians during their current practice. In dermatology, novel diagnostics for cellulitis are needed in order to decrease the high misdiagnosis rate, prevent unnecessary hospitalizations and reduce overuse of antibiotics. In ophthalmology, a therapeutic strategy to stop myopia progression and therefore prevent high myopia development and its severe long-term effects is required. Solutions to either of these problems depend on the assemblage of multiple novel technologies. More importantly, the solutions rely on scientists and engineers with multidisciplinary background and expertise in fields such as biomedical optics, biophysics, photochemistry, biology, biomedical engineering, and biomechanics to actively engage in dialogue with their clinician colleagues to first understand the problem and then consistently plan for relevant proof-of-concept experiments and successful partnerships with industry.

Over the next decade, translational research will become an essential mechanism to seed and sustain future innovation in academia, bringing better and more cost effective new treatments and diagnostics to patients in need. To this effect and based on the continuous increase of biomedical optics and photonics technologies worldwide, scientists and engineers will have tremendous opportunities to engage with clinicians and patients and establish solid partnerships with industry. Innovative training programs in translational sciences will lay the

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ground work for an intellectual home where new generations of scientists, engineers and clinicians from academia will be able to consistently reach out to their peers in industry to solve important problems in medicine and human health.

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## Disclosures

The authors declare that there are no conflicts of interest related to this article.

