Important contributions are being made in laboratories, clinical settings and communities as we strive to improve patient care. These efforts are inherently interdisciplinary and multiprofessional, requiring collaborations and partnerships across various locations.(1) However, even as endeavors to cultivate new knowledge and apply it to health-related problems continue, some have considered the results to be inefficient. New discoveries in the lab often take decades to develop into therapies with broad applicability to human populations.(1,2) Community health needs typically are not investigated as quickly as topics of basic research.(2) Additionally, sharing knowledge among basic and clinical researchers has been difficult, as has been its practical application toward improving health outcomes.(1-3)

Defining Research Realms
Basic research can be difficult when simplistic preclinical animal models translate poorly to human disease, as is often the case. Species differences provide potentially insurmountable challenges for supportive care modalities in humans.(3,4) Barriers in clinical research begin with recruiting and maintaining a homogenous patient population, especially in the specialized area of critical care, which inherently suffers from a lack of predictability and reliability. Quality-tested, reproducible results are ethically and logistically difficult to execute.(5-7)

Translational research (TR) continues to evolve as an academic, scientific discipline, seeking to remove these barriers and shift discovery more efficiently and effectively into clinical application.(1,3) TR investigators work to close the knowledge gaps among the basic science laboratory, clinical research, and application levels. The TR continuum extends from basic research (e.g., chemistry of viral gene regulation) to practical application and implementation, followed by dissemination and policy studies (e.g., vaccine delivery).(1,3,4,8) TR is often broadly subdivided and defined at two levels, type 1 (T1) and type 2 (T2). T1 often refers to the “bench to bedside” spectrum of research characterized as “effective translation of the new knowledge, mechanisms, and techniques generated by advances in basic science research into new approaches for prevention, diagnosis, and treatment of disease which is essential for improving
health.”(8) The endpoint of T1 research is the production of a clinically useful, novel and promising treatment commercialized to a broad population of human subjects. The endpoint produced by T1 becomes the starting point for T2 research initiatives.(9,10)

T2 research translates new evidence-based results and/or treatments learned in T1 investigations into practice by ensuring they are correctly implemented and actually reach the intended patients or populations.(9) Investigators in public health whose studies focus on healthcare outcomes have a specific interest in identifying means of improving accessibility, reorganizing and coordinating care systems, facilitating change in patient and clinician behaviors, and strengthening patient relationships with healthcare providers, in addition to addressing other endpoints that close gaps and improve quality of care.(10) T2 researchers continually pursue the most effective means for achieving knowledge transfers across all medical disciplines, while also struggling with social factors (e.g., unpredictable human behaviors, change in organizational infrastructure and resource limitations).(11)

**Models of Success**

Among the success stories in T2 research, few have received as much praise from the critical care community as the Keystone ICU project,(3,6) which demonstrated the ability to reduce catheter-related bloodstream infections by 66% in more than 100 participating ICUs. Following the implementation and integration of an evidence-based intervention into practice is a most noteworthy achievement.(12,13) Several institutions in multiple countries have ongoing research collaborations and promote the formation of critical care clinical trials groups to achieve positive outcomes.(5,6) Through the results of the Keystone ICU project, we have hopeful confirmation that – by working within a multiprofessional team of researchers and clinicians – we can implement guidelines and achieve nearabsolute compliance. This diligence can and should produce robust results that eventually reduce morbidity and mortality rates for intensive care patients.

**Challenges in Bench to Bedside**

Certain medical specialty fields, such as oncology, rheumatology and cardiology, have seen improvements in the “bench to bedside” advances from TR, but critical care medicine is relatively new and still evolving.(7,11,14) While millions of dollars of support are poured into basic science and clinical trials, relatively few pharmacologic interventions have translated into measurable clinical benefit for critically ill patients.(3) Critical care practitioners are well versed in the potential roadblocks of conducting both T1 and T2 research in the intensive care unit (ICU) setting, as successes and suboptimal results or failures in new research targets are readily found in peer-reviewed journals.(1,6)

In recent years, TR in critical care medicine has produced several robust biomarkers and prognostic markers to advance patient care, but has not yet produced novel pharmacologic therapies. Instead, translational scientists and researchers have tested established therapies for alternative clinical indications in the hopes of deriving some benefit for the critical care population.
The HARP Study. The Hydroxymethylglutaryl-CoA Reductase Inhibition with Simvastatin in Acute Lung Injury to Reduce Pulmonary Dysfunction (HARP) study stands as an example of T1 research deriving new use from established compounds. Hydroxymethylglutaryl-CoA reductase inhibitors have been gaining investigational popularity in many areas of medicine (aside from cardiology), including critical care. Since 2009, simvastatin has shown promise in reducing the number and activity of neutrophils in the alveolar space and in reducing cytokines in bronchoalveolar lavage fluid. This was true in vitro and in animal in vivo lipopolysaccharide models of acute lung injury (ALI), compared to untreated controls.(15)

HARP investigators utilized a bench-top therapy (simvastatin) in a novel indication (ALI) and patient population (critically ill patients).(15) A proof-of-concept trial in 60 patients with established early onset (<48 hours) ALI compared simvastatin, 80 mg per day, to placebo. The results, published in 2011, demonstrated simvastatin-treated patients had modest improvement in pulmonary functions of oxygenation and respiratory mechanics 14 days after randomization; however, this primary endpoint did not reach statistical significance. Noteworthy were early reductions in pulmonary and systemic markers of inflammation, thought to produce significant improvements in nonpulmonary organ dysfunction in statin-treated patients.(3,15) Because death from ALI is commonly attributed to multiorgan dysfunction, the nonpulmonary organ findings led the team to conduct further T1 research, with the HARP-2 study currently underway.

PASS and Sepsis. The clinical utility of multiple biomarkers also has been investigated by T1 and T2 sepsis researchers. Procalcitonin (PCT), a calcitonin precursor hormone, has emerged as a potential tool in the bedside management of septic patients. Its use in the diagnosis of sepsis remains debatable due to varying results of specificity in ICU patients. A 2004 investigation that included all types of medical patients found PCT to have a higher sensitivity (85% vs 75%) and specificity (81% vs 67%) than the biomarker C-reactive protein.(16) Contrary to these findings, a 2007 systematic review of 18 studies in critically ill patients estimated the diagnostic accuracy, with mean sensitivity and specificity values of 71%.(17) Although the specificity of PCT use in diagnosing sepsis is still debated, biomarkers that impact patient outcomes are under investigation as a potential guide to antimicrobial stewardship.

The Procalcitonin and Survival Study (PASS) involved more than 1,200 critically ill patients at nine ICUs across Denmark.(18) Investigators developed guidelines for obligatory antimicrobial intervention based on the reporting of daily PCT levels in septic ICU patients. The comparator arm was a standard-of-care-only group; antimicrobial therapy was guided according to clinical guidelines, and investigators were blinded to PCT levels. The primary endpoint of death at 28 days after enrollment did not differ between groups. In fact, a secondary outcome, length of stay in the ICU, was increased by one day in the PCT-guided arm. Despite leading to a significantly higher use of antimicrobials, the PCT-guided strategy did not lead to earlier, appropriate initiation of antimicrobials, which has been demonstrated repeatedly to lead to an improved prognosis.
The PASS investigators pieced together several limiting factors for the neutral and suboptimal outcomes observed (except in patients with bloodstream infections). The shortcomings of this and many other investigations are eerily similar and nearly identical to the reasons T2 translational research needs more recognition and emphasis among academic researchers and policy makers; multiple barriers prevent therapies from reaching patients as they were originally intended at the bench or in a controlled research environment.

**Improving Bench to Bedside**

In a 2003 U.S. report, only about 50% of surveyed patients received recommended evidence-based medical care.(19) The development and publication of evidence-based guidelines are rarely integrated into bedside practice in a timely fashion. If this does occur, it often does not lead to changes in clinical behavior.(11,14) The slow and challenging process of changing practice is a phenomenon recognized by all members of the multiprofessional healthcare team, especially in critical care.

One can argue the bench-to-bedside enterprise is a failure if the healthcare system cannot close the gaps in achieving optimal healthcare outcomes. Further testing of the practical implementation and delivery of developed treatments in T1 research may shrink the gap. Simultaneously, in the T2 phases of clinical research, planning strategies to overcome political as well as institutional barriers would increase adherence to guidelines and recommendations by policy makers and administrators. This combination of efforts could allow beneficial treatments to reach the critical care community in a more timely and steadfast manner.

**References:**


Disclosures:

* Author has no disclosures to report

** Author has no disclosures to report