Successfully Accelerating Translational Research at an Academic Medical Center: The University of Michigan-Coulter Translational Research Partnership Program

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Abstract

Translational research encompasses the effective movement of new knowledge and discoveries into new approaches for prevention, diagnosis, and treatment of disease. There are many roadblocks to successful bench to bedside research, but few have received as much recent attention as the "valley of death." The valley of death refers to the lack of funding and support for research that moves basic science discoveries into diagnostics, devices, and treatments in humans, and is ascribed to be the result of companies unwilling to fund research development that may not result in a drug or device that will be utilized in the clinic and conversely, the fact that researchers have no access to the funding needed to carry out preclinical and early clinical development to demonstrate potential efficacy in humans. The valley of death also exists because bridging the translational gap is dependent on successfully managing an additional four risks: scientific, intellectual property, market, and regulatory. The University of Michigan (UM) has partnered with the Wallace H. Coulter Foundation (CF) to create a model providing an infrastructure to overcome these risks. This model is easily adoptable to other academic medical centers (AMCs). Clin Trans Sci 2010; Volume 3: 316–318

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Introduction

The Institute of Medicine (IOM) through its Clinical Research Roundtable series beginning in 2000 identified translational research as crucial to improving the health of the nation. These meetings were the first to define blocks to the translation of discovery to patients: The T1 block acknowledged the difficulties of moving a laboratory finding into patients. The T2 blockade referred to the difficulties of adopting new, approved drugs and devices into general medical practice.[1,2] The translational paradigm has since been subdivided into four steps (see *Figure 1*): T1 research seeks to move a basic discovery into a candidate health application; T2 research assesses the value of T1 application for health practice leading to the development of evidence-based guidelines; T3 research attempts to move evidence-based guidelines into health practice through delivery, dissemination, and diffusion research; T4 research seeks to evaluate the "real-world" health outcomes of a T1 application in practice.[2,3] Translational research encompasses the effective movement of new knowledge and discoveries into new approaches for prevention, diagnosis, and treatment of disease.[1–3]

Within the T1 blockage sits the translational gap known as the "valley of death."[4,5] The valley of death refers to the lack of funding and support for research that moves basic science discoveries into diagnostics, devices, and treatments in humans (see *Figure 2*). Traditionally, the valley of death is ascribed to be the result of the National Institutes of Health and pharmaceutical companies not willing to fund research development that may not result in a drug or device that will be utilized in the clinic and conversely, the fact that researchers do not have access to the funding needed to carry out the preclinical and early clinical development to demonstrate potential efficacy in humans.

Funding, however, is not the only reason the valley of death exists. Bridging the translational gap is dependent on successfully managing an additional four risks: scientific, intellectual property (IP), market (commercialization), and regulatory. Scientific risk includes all of the proof of concept issues that arise as part of preclinical and clinical investigations, including target validation as well as eventual safety testing. IP includes novelty of concept, existing patents, and competitive technologies. Commercialization risk encompasses whether the product based on discovery will be a market leader or follower, the size of the market, time to market, and investment needed for successful launch. Regulatory needs require understanding the appropriate path and Food and Drug Administration (FDA) requirements necessary for approval.

Since 2005, the University of Michigan (UM) has partnered with the Wallace H. Coulter Foundation (CF) to not only fund research that spans the valley of death but also create a model that provide an infrastructure for programmatic support to overcome the scientific, IP, market, and regulatory risks.

University of Michigan-Coulter Foundation (UM-CF) Program

The overall goal of the Coulter Translational Research Partnership Program is to achieve excellence and sustainability in translational research in biomedical engineering in perpetuity. The CF funded similar programs at eight other academic institutions. Each institution was provided with an initial grant of $580,000 per year with the intent to fund each for 5 years. Starting in the second year of funding this was raised to $1 million per year. In years 4 and 5, the program was further supplemented with $100,000 per year by the Michigan Institute for Clinical and Health Research (MICHR) that houses the Clinical and Translational Science Award (CTSA) of the UM.

The goal of the UM-CF program is to support collaborative research that addresses unmet clinical needs and leads to improvements in health care and to commercial products. The program supports collaborative translational research projects that involve co-investigators from the Department

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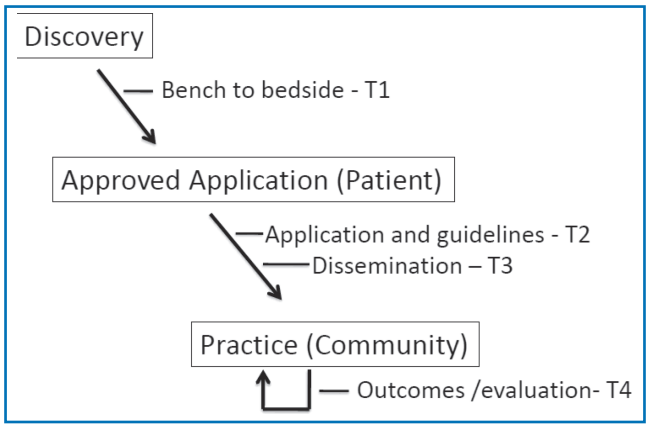

Figure 1. The translational continuum. The translational paradigm has been subdivided into four steps. T1 research is the traditional bench to bedside work that leads to approval of a drug, device, or diagnostic. T2 research assesses the value of the approved application in medical practice and establishes guidelines for use. T3 research studies the movement of evidence-based guidelines into health practice through delivery, dissemination, and diffusion research. T4 research evaluates the "real-world" health outcomes of a T1 application in practice.[2]

of Biomedical Engineering (BME) and a clinical department to create translational teams. Examples of desirable outcomes include inventions, patents, improved diagnosis and treatment of disease, commercial partnerships, start-up companies, and follow-on funding targeted toward these same outcomes.

Project selection involves more than just funding the best peer-reviewed translational science. To be chosen for the program, each potential project is assessed for market potential, IP, regulatory strategy, reimbursement, and product development activities. The program also relies heavily upon the Coulter Oversight Committee (OC) at Michigan for project selection, monitoring, and mentoring.

Process for choosing projects: A Call for Proposals is issued in the fall and faculty with both full-time and part-time appointments in the BME Department are encouraged to submit a proposal. Proposals are "triaged" by the OC to assess the translational nature of each project. Finalists are invited to make presentations to the OC at a meeting in early spring where funding is determined for the year. Project cycles run from April 1 through March 31.

Projects are selected, reviewed, and assessed by the OC. The mission of the OC is to ensure the quality of translational projects and the sustainability of the Translational Partnership Program. The OC consists of The Chair of the BME (Committee Chair), the Senior Associate Dean for Research of the Medical School, a senior-level research dean from the College of Engineering, one representative from the local business community experienced with entrepreneurial activity in biomedical products, one representative from the venture capital community experienced in early-stage biomedical investing, representatives from the UM's Office of Technology Transfer, one clinical physician reviewer qualified to judge the applications based upon their clinical relevance, one regulatory affairs specialist as well as scientific/technical reviewers as required to provide needed expertise. The Coulter Program Director (CPD) serves as an *ex officio* member of the OC. The OC performs the following specific roles: assist with team and proposal solicitation and development, review and select individual translational research projects that will be funded annually, assess quarterly reports for the projects and the program, evaluate the project portfolio, conduct an annual "post-mortem" on killed projects, and provide mentoring to teams. This mentoring may involve individual meetings, identification of specific technical, regulatory, marketing or strategic expertise, and introductions to possible sources of follow-on funding. The OC is also meant to provide regular feedback to the Program principal investigator (PI), co-principal investigator (Co-PI), and CPD about the program, program evaluation, and provide updates to the senior University administration as needed or requested.

An important part of the CPD and the OC is to provide mentoring to the teams around all areas of risk. This mentoring involves individual meetings, identification of specific technical, regulatory, marketing or strategic expertise, and introductions to possible sources of follow-on funding. Projects are funded initially for one year. Projects that met goals are eligible for further funding. Projects that are not successful are stopped. The OC then conducts an annual "post-mortem" on killed projects to learn potential lessons to apply when identifying future projects.

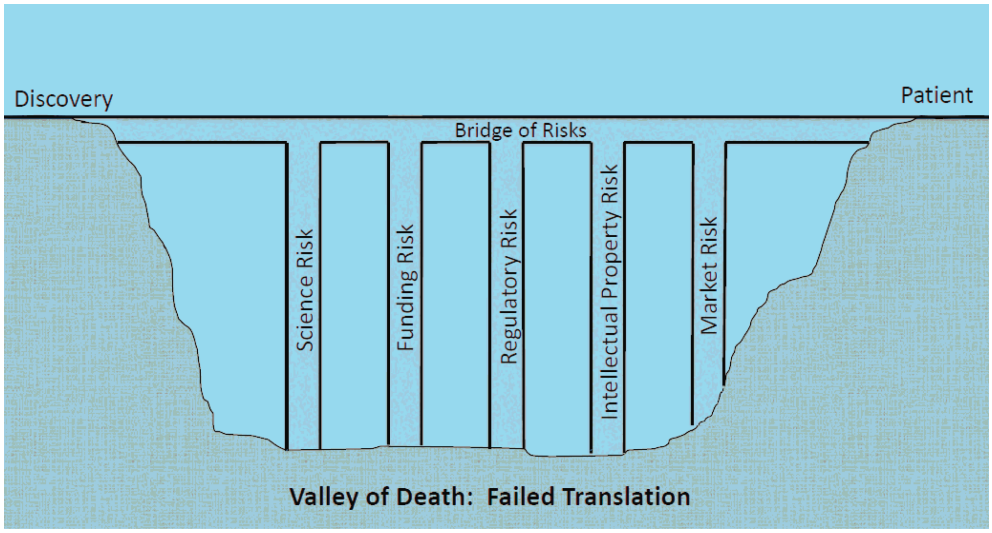

Figure 2. Bridging the valley of death. The University of Michigan-Coulter Foundation Program addresses the major risks necessary to translate a discovery to the clinic. These include scientific peer review, identifying funding, identifying potential markets, and managing intellectual property and regulatory risks.

Scientific risk

Is addressed through peer review. Applications are chosen for the quality of the underlying hypothesis and/or discovery, as well as the quality of the preliminary data. The research plan as well as the quality of the investigators is judged. In addition, the ability of the individual faculty to work as a team is assessed through the written application as well as at oral presentations. The research plan had to outline specific issues

that had to be overcome to bring the concept to market and had to be associated with specific milestones. Applications without the appropriate scientific rigor are not funded.

IP risk
Is assessed in several ways by the UM Office of Tech Transfer as well as the OC. Novelty of the discovery is assessed through patent searches. Infringing IP is identified and assessment of freedom to operate is performed. If there is existing IP, expiration date of the patents is explored. Competitive technologies currently in the market or being brought to market are identified. Research teams are asked to identify other research teams pursuing technology in the area. Applications without identifiable IP are not funded.

Market/commercialization risk
Is assessed by the research teams and the OC committee. Special emphasis is given to this area by ad hoc clinical experts as well as the members of the OC from the business community and the venture capital community. First and foremost, the discovery research has to be framed to deliver a commercial product with a defined market. The deliverable product is preferred to be a market leader or is thought to have the potential to displace an existing product. An estimate of the earliest likely timeframe that a product, whether it is a drug, device, or diagnostic, could make it to market is made. A critical question is whether a market will still exist in the time frame of development.

Regulatory risk
Is determined by the UM regulatory expert. The likely regulatory path (e.g., 510(k), Pre-market Approval Application (PMA), none) is identified. Examples of recent similar products and their path to approval are sought. Types of clinical trials are identified for these products. FDA guidance documents that cover the potential product are identified and subsequent discussions with the FDA are facilitated.

Funding risk
Is determined. A plan for funding after the Coulter award expired is required for each successful project. Funding plans include National Institutes of Health (NIH)-R01 and other federal grants, Small Business Innovation Research (SBIR)/ Small Business Technology Transfer Research Program (STTR), Venture Capital, licenses, and philanthropy. A preliminary assessment of the typical necessary capital for development of a product is made. Applications without a follow-on funding plan are not funded.

Having completed five rounds of applications, 19 projects have been funded to date. The result of these risk assessments were that in 2006, 4 of 6 applications were selected for funding, in 2007, 6 of 14 applications were selected for funding, in 2008, 6 of 13 applications were selected for funding, in 2009, 7 of 18 applications were selected for funding, and in 2010, 6 of 16 applications were selected for funding. Total Coulter funding for projects has been $3,174,928. Total nonproject related research grants generated has been $7 million. This has included both SBIR as well as R01 grant funding. The amount of funding received for the purpose of advancing projects through the translational continuum (follow-on funding received) has been $21,700,000, the majority in venture capital funding for start-up companies. In financial terms, this is a return on investment of nine to one in just 4 years. From an IP perspective, two disclosures, seven provisional patent applications, and 13 full patent applications have been generated. One example of a successful start-up is HistoSonics Inc., a new medical device company that is developing a noninvasive image guided and robotic tissue ablation technology. Histotripsy was developed by UM faculty as a platform that will potentially replace traditional surgical and minimally invasive methods to reduce patient trauma and health care costs. The first clinical application will be treatment of benign prostatic hyperplasia, a prevalent condition in older men. A second start-up company based on discoveries of UM faculty is Life Magnetics, Inc. Life Magnetics is developing an *in vitro* diagnostic device and cartridge for rapidly determining the antimicrobial susceptibility of bacterial infections utilizing an instrument that can perform these tests in a time-scale of hours rather than days.

Bridging the valley of death requires more than simple funding. The UM-CF Partnership Program provides a model of institutional support that provides investigators a framework to successfully bridge the gap between the bench and the bedside.

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