

As future scientists in academic, industrial and governmental settings, graduate students will increasingly be called upon to play roles in the conception, development, testing, validation and regulatory approval of experimental devices, drugs, and services, as well as in the formation of new and effective health care policies. The effective establishment of intellectual property is often essential to achieving success in translating bench findings to the bedside and marketplace. Understanding the pathways and processes of start-up company formation provides opportunities to pursue innovations. Evidenced based medicine and personalized medicine are emerging arenas in which all scientists associated with the health care, pharma and biotech sectors will be expected to participate. The vitality of the American health care system depends upon a scientific workforce skilled in creative discovery, innovation, clinical testing, and entrepreneurship. Graduate and medical students presently encounter little formal training in the core knowledge that underlies the domain of translational science nor do they gain early in their training the essential conceptual frameworks and skill sets required to appreciate or execute the development of product concepts through to the patient bedside.

The National Institute of Health has formed the National Center for Advancing Translational Science [NCATS], which together with the previous emphasis on the NIH RoadMap, underscores the importance of translational science as an engine for economic development. The Federal emphasis on translational science is mirrored by global pharmaceutical companies increasingly looking to academia for fundamental insights into basic aspects of human biology that may lead to new devices, drugs and procedures. The business development units of a host of big pharma companies have now developed partnerships with major universities. Thus, the topic of how best to innovate and bring new health care products to the patient, pharmacy, and drug store shelf, represents an area of current national and international focus and an educational area in which UVA's graduates will increasingly be called upon to engage. The University of Virginia affirms its historic role in leading curriculum development to meet national priorities and creating leaders who can excel in emerging arenas. Translational and regulatory science is a field of great promise both academically and from the perspective of market need and job opportunities.

In the varied career paths that UVA Medical School graduates now enter, a thorough understanding is required of business, legal and regulatory issues that shape the key milestones in the translational science pathway from idea to product. The Essentials of Translational Science Curriculum will introduce students to topics that will help them be leaders and innovators in health care, think creatively about new product concepts and services, develop skills that will allow them to seize opportunities for intellectual property creation, promote proof-of-concept research, partner successfully with industrial sponsors, foster commercialization and entrepreneurship, and strengthen the flow of medical discoveries into society to optimize their societal impact. Graduate and medical students who understand the legal and regulatory environments that underlie translational science will be better equipped to shape innovations that will transform future medical practice.

This curriculum emphasizes lectures by experts, case study analyses, and interdisciplinary learning opportunities with basic scientist inventors, patent lawyers, clinical trials design coordinators, business and

management leaders, angel and venture capitalists, entrepreneurs, and FDA regulators. The curriculum also takes advantage of highly interactive learning environments in laboratories, case studies, and problem solving exercises. A range of teaching techniques are encountered to engage and immerse students in stimulating active learning contexts.

\_\_\_\_\_ The text: “Engines of Innovation, The Entrepreneurial University in the Twenty-First Century” by Holden Thorp and Buck Goldstein and “Zero to One, by Peter Thiele will be the principal texts. Student power point presentations on the chapters of these texts will constitute a part of the course grade.

\_\_\_\_\_. Students will write essays on several assigned topics as part of the final grade.

Translational science is a complex of intellectual disciplines which focus on the discovery of new basic scientific knowledge and its effective dissemination and utilization by society. Basic research is the cornerstone from which innovation arises. Translational science may be modeled as a cycle [Fig 1] that begins with Discovery, moves through Characterization and Validation stages, the Development of Enabling Tools, Marketing and Acceptability Research, Creation of the new Drug or Device prototype, Precision Manufacturing under GLP or GMP, Pre-clinical Evaluation, Clinical Trials, Outcomes Assessment and Regulatory Agency Interactions, Product Launch, and Post-Introduction Monitoring. The process is envisioned as a continuum where a new product, once in use, is likely to generate new ideas and be supplanted by new discoveries and improvements...thus translational science may be seen as a dynamic, cyclical, innovation process of continuing improvement in products and services. Importantly, TS is a group effort...where cooperating teams of scientists, patenting personnel, translational research navigators, clinicians, statisticians, finance,

## Product Development Cycle of a Biotherapeutic: The Communities of Science, Intellectual Property, Finance, Manufacturing and Marketing Represent a Continuum of Co-operating Teams and Capital.



**Fig. 1**

manufacturing, and marketing personnel add value to a product concept through defined steps which advance the product concept toward societal impact. Figure 1 defines stages in the development of a new biotherapeutic drug. On this cycle the stages most likely to result in new inventions and intellectual property [IP] are noted.

The curriculum in translational science will lead to an understanding of the process of translational science as a whole, as it applies to drugs, devices, and clinical procedures and policies. The curriculum in translational science will also develop skill sets and a knowledge base in areas critical to successful execution of translational science initiatives.

The metrics for measuring effective translational science activities within a major research medical center include the capture of intellectual property through patenting; prototype creation; proof-of-concept research that validates a socially useful product or policy concept; successful partnering with industrial, partnerships with angel and venture groups to commercialize innovations; the careful and effective conduct of clinical and consumer trials; and effective utilization of FDA resources and guidance to insure safety and efficacy of inventions.

. The Curriculum in Translational Science consists of learning modules each of which focus on a stage of the Translational Science Cycle. Scholarship will focus on the text: “Engines of Innovation, The Entrepreneurial University in the Twenty-First Century” by Holden Thorp and Buck Goldstein and “Zero To One” by Peter Thiel. These books are available in the Newcome Hall Book store. Student presentations on the chapters of this text will constitute a part of the course grade.

<i>Topics</i>	<i>Leaders/Co-lecturers</i>
<p>Content – Mass spectrometry is a key element of target discovery and validation and may also be used in later steps such as clinical trials and outcome assessment. The MS module will lay the fundamental principles involved in choosing when to use mass spectrometry as an analytical tool, what mass spectrometers are available, and what upstream elements are necessary to obtain quality data. The endpoint of the lecture should find the student with the necessary knowledge for using mass spectrometry in their biological research.</p> <p>Content – MALDI-TOF is a robust MS technique that</p>	

<b>Topics</b>	<b>Leaders/Co-lecturers</b>
<p>can be used for QC of proteins, peptides and many small molecules (such as synthesis, purification, etc). This instrument is open access in the MS Core and students will be trained and certified in its use as a QC tool. Additionally, MS data can appear complex. Students will be exposed to fundamental data and its display to achieve a basic working knowledge so as to be able to assess their data for quality and future experimental planning.</p> <p>Monoclonal antibodies have significant application to both <i>in vitro</i> and <i>in vivo</i> technologies and many have been developed as tools of significant clinical value in both diagnostics and treatment. Students will learn the general considerations and basic strategies necessary for classical hybridoma construction in order to develop and characterize monoclonal antibodies to target antigens.</p> <p>escription: Cytomics is the study of cell systems at the single cell level. Advancing technologies are producing novel and innovative tools and instrumentation to be able to interrogate cells at the single cell level at a level of complexity and depth not previously available. This section will introduce the student to these emerging technologies and their potential applications in research. Technologies such as imaging flow cytometers, Flow Mass Cytometry, and high throughput cellular analysis at the RNA level using flow cytometry are some examples of what will be covered. There will also be lab</p>	

<i>Topics</i>	<i>Leaders/Co-lecturers</i>
<p>demonstrations of the imaging and mass cytometry instrumentation.</p> <p>Interdisciplinary teams generally execute translational research in the biomedical sciences. Building, facilitating and sustaining these kinds of teams can be challenging, due to disciplinary differences in culture, conflicts between individual and collective (i.e, project needs), identifying talent, and addressing personality differences. UVa is the lead institution for one of the largest NIH funded interdisciplinary research consortia. This lecture will present lessons learned in building and sustaining team research.</p> <p>This seminar will trace the development of a sperm specific biomarker protein, SP-10, from its discovery, validation, and patenting, through corporate partnering, clinical and consumer trials and on to FDA interactions and immunodiagnostic device approval. In January of 2008 the United States Food and Drug Administration approved the first point-of-care test for monitoring sperm following vasectomy. This was followed by the FDA approval of SpermCheck Fertility for detecting subfertility due to sperm count in 2010 and the December, 2012 Health Canada clearance of this device. These forward flow devices are the only highly accurate, approved, immunodiagnostic tests for detecting trace numbers of sperm.</p>	

<b>Topics</b>	<b>Leaders/Co-lecturers</b>
<p>Leading up to this new clinical product were basic and preclinical research on the biomarker analyte in the devices, the SP-10 protein, and the ACRV1 gene, its pattern of expression, and various aspects of cellular, molecular and reproductive physiology involving the SP-10 protein. The SP-10 protein was discovered and cloned in man, baboons, monkeys and mouse and thereafter it was shown that the SP-10 protein was selectively expressed in human spermatids and in sperm. Studies of human testis sections localized the SP-10 protein with a monoclonal antibody only in spermatids and SP-10 mRNAs, using in situ hybridization, were similarly localized only in post-meiotic cells. Studies of SP-10 expression were also undertaken with all major organs in the primate body, and the SP-10 gene was found to be only transcribed in the testis. Following cloning of the mouse gene for SP-10 transgenic mice were created that contained the SP-10 promoter and a green fluorescence protein [GFP] reporter. These transgenic mice revealed that SP-10 was expressed in a stage specific manner during the onset of spermatogenesis only in testis and in spermatids.</p> <p>To be a useful biomarker for a clinical assay, the SP-10 protein had to be relatively soluble and methods were developed to release it from its intra-acrosomal location in the sperm head so that it could be measured in solution. Once it was realized that the SP-10 protein could be released from the sperm head with mild detergents, pairs of monoclonal antibodies were then selected that recognized different parts of the SP-10 molecule and an assay that captured the SP-10 protein was developed. Also the gene for human SP-10 was expressed as a</p>	

<i>Topics</i>	<i>Leaders/Co-lecturers</i>
<p>recombinant protein in bacteria. In this form it could serve as an assay standard. This assay proved to be highly sensitive, capable of detecting as low as 40 ng SP-10/ml. Moreover, a direct correlation was found between the concentration of SP-10 and the concentration of sperm.</p> <p>The issuance and prosecution of key patents were essential to the eventual commercialization of this technology. With the discovery, clinical testing, and FDA approval of the SpermCheck Vasectomy assay, the paradigm for sperm monitoring in infertile couples and following vasectomy now shifts from the microscope to a simple, easy to use, highly sensitive, hand held device that affords privacy and cost savings.</p> <p>Some references for this talk:</p> <p><u>Herr, J.C.</u>, C.J. Flickinger, M. Homyk, K. Klotz, E. John 1990 Biochemical and Morphological Characterization of the Intra-acrosomal Antigen SP-10 from Human Sperm. Biol. Reprod. <u>42</u>: 181-193.</p> <p>Kurth, B.E., K. Klotz, C.J. Flickinger, <u>J.C. Herr</u> 1991 Localization of Sperm Antigen SP- 10 During the Six Stages of the Cycle of the Seminiferous Epithelium in Man. Biol. Reprod. <u>44</u>: 814-821.</p> <p>Foster, J.A. and <u>J.C. Herr</u> 1992 Interactions of human sperm acrosomal protein SP-10 with the acrosomal membranes. Biol. Reprod. <u>46</u>: 981-990.</p> <p>Freemerman, A.J., <u>R.M. Wright</u>, C.J. Flickinger, <u>J.C. Herr</u> 1994 Tissue Specificity of the Acrosomal Protein SP-10: A Contraceptive</p>	

<i>Topics</i>	<i>Leaders/Co-lecturers</i>
<p>Vaccine Candidate Molecule. Biol. of Reprod. 50:615-621.</p> <p>P. Prabhakara Reddi, Marko Kallio, and <u>John C. Herr</u> 1999 Green fluorescent protein as a reporter for promoter analysis of testis-specific genes in transgenic mice. Methods in Enzymology 302: 272-284.</p> <p>Kenneth L. Klotz, Michael A. Coppola, Michel Labrecque, Victor M. Brugh III, Kim Ramsey Kyung-ah Kim, Mark R. Conaway Stuart S. Howards, Charles J. Flickinger, and <u>John C. Herr</u> 2008 Clinical and Consumer Trial Performance of SpermCheck<sup>®</sup> Vasectomy, a Sensitive Immunodiagnostic Home Test that Qualitatively Detects Low Concentrations of Sperm Following Vasectomy. J. Urology Dec;180(6):2569-76. Epub 2008 Oct 19. [cover article].</p> <p>Michael A. Coppola, Kenneth L. Klotz, Kyung-ah Kim, Jagathpala Shetty, Stuart S. Howards, Charles J. Flickinger, and John C. Herr. 2010 SpermCheck<sup>®</sup> Fertility, an Immunodiagnostic Home Test that Detects Normozoospermia and Severe Oligozoospermia. Human Reproduction 25: 853-86 [cover article].</p> <p>U.S. Patent 5,605,803, Issued Feb. 25, 1997. Title: "Human Sperm Diagnostic" Inventors: J. C. Herr and R. M. Wright.</p> <hr/> <p>Description: This lecture module will introduce students to the origins of bioinformatics, and how contemporary high-throughput genomic studies can drive the discovery phase in a translational science research program. The lecture will introduce students to bioinformatics resources and statistical</p>	

<i>Topics</i>	<i>Leaders/Co-lecturers</i>
<p>concepts for large-scale gene expression studies, paving the way for the laboratory section where students will engage in a hands-on data analysis.</p> <p>Reading Assignments/Handouts – 35 USC 101, 102, 103, 112</p> <p>Objective – To provide students with basic familiarity with intellectual capital, intellectual assets, and intellectual property including patents, trademarks, copyrights, and trade secrets.</p> <p>Reading Assignments/Handouts – The Law of Unintended Consequences; Innovation’s Golden Goose; 35 USC 200; Mission Statement of NIH, “Managing IP in the Public Interest”; “Profiting from Technological Innovation”</p> <p>Objective – To provide students with an overview of the impetus behind and practice of University technology commercialization.</p> <p>Reading Assignments/Handouts – “Patentable Inventions Versus Unpatentable: How to Assess and Decide”</p> <p>Reading Assignments/Handouts – Razgaitis Table, Discounted Cash Flow spreadsheet</p> <p>Objective - To provide students with a framework for evaluating an early stage technology on its technical/scientific, commercial, and intellectual property bases.</p>	<p>Michael Straighttiff</p>

<b>Topics</b>	<b>Leaders/Co-lecturers</b>
<p>Objective - Students will be presented with several early stage technology valuation frameworks – comparables, discounted cash flow, and the venture capital method.</p> <p>Course project – “live” invention disclosure assessment. Students could be divided in to groups and provided with an invention disclosure to evaluate. Each participating student will execute a non-disclosure agreement.</p> <p>Used during the design stage of medical devices, realistic computer simulation can provide valuable information about their safety and limitations, can guide and focus the emphasis of subsequent clinical trials, and can rule out ineffective design scenarios in a cost-effective manner prior to human use. In January 2008, our computer simulator of the human metabolic system in diabetes became the first computer tool accepted by the FDA as a substitute to animal trials in the pre-clinical testing of artificial pancreas systems. This allowed efficient and cost-effective <i>in silico</i> experiments to be performed at the level needed for FDA regulatory approval of human clinical trials and accelerated the development of closed-loop control systems. In 2009, this simulation technology was licensed by a company in Charlottesville, which has since run numerous simulation experiments for academic and industrial applications. Three years later, a paradigm shift in artificial pancreas development is apparent: animal trials are no longer performed in this area; virtually all pre-clinical studies are run using our simulation environment. To date, there is no other simulation system receiving comparable level of FDA acceptance. In this presentation we will review the scientific and engineering development of the UVA simulation environment, and will highlight the requirements that needed to be met for its FDA</p>	

<i>Topics</i>	<i>Leaders/Co-lecturers</i>
approval. An interactive session will be offered to introduce some of the capabilities of in-silico design of insulin treatment strategies for diabetes.	

<i>Topics</i>	<i>Leaders/Co-lecturers</i>
<p>1 The objective of this module is to give students an overview of the basic functioning of business through a discussion of general business theory, Entrepreneurial thinking and two cases demonstrating the complexity of and selling drugs in a market where the customer neither chooses the product or pays for it and is told by the FDA which products they may receive. Lastly the Lab will be a field trip to a business where the students will have an opportunity to challenge themselves to see if “they” could run this business.</p> <p>The topics and the Lab will be broken up as follows.</p> <p><b>General Overview of Business Formation [April 20]</b></p> <ul style="list-style-type: none"> <li>-Limited liability. Why doing business in America is not like other parts of the world.</li> <li>-Pros and cons of for-profit and not-for-profit companies. Why is profit good? Where does it break down?</li> <li>-If Capitalism is bad, what’s the alternative?</li> <li>-If you are going to change the world become an Entrepreneur! Agree? Disagree?</li> </ul>	

	<p>-What makes an Entrepreneur entrepreneurial?</p> <p><b>Case Study: The Medicines Co –Angiomax [April 23] Handout to read before class</b></p> <p>-Each student will be expected to come to class having read the case and based on the information provided come up with a justification for the price at which Angiomax should be sold.</p> <p>-Who is the customer? Be prepared to explain as the Chief Marketing Officer of the Medicines Co How would you promote this drug and to whom?</p> <p><b>How To Launch Your Business Idea April 24</b></p>	
--	---	--

--	--	--

	<i>Topics</i>	<i>Leaders/Co-lecturers</i>
1	<p>This presentation will explore FDA's legal authority and the regulatory rubric for approval of a biomedical product. We will discuss the differences between drug, devices and biologics approval and regulation. We will also see how the interplay and overlap with other agencies affects product approval and regulation.</p> <p>Learn what it takes to be successful in getting a product cleared through the FDA.</p>	

	<b>Topics</b>	<b>Leaders/Co-lecturers</b>
1	<p>Local biotech entrepreneurs to tell their start-up sagas: Microlab, and Setagon</p> <p>Microfluidic or 'Lab-on-a-chip' systems offer new potential in terms of expediting chemical and biochemical analysis by seamlessly integrating sample preparation with analytical steps. The development of chemical fluidic circuits in glass or polymeric substrates with features in the low Reynold's Number regime allows for enhanced kinetics with reactions typically limited by diffusion. Compressing multiple chemical steps into a credit card-sized device requires the engineering of new instrumentation that integrates the capabilities of numerous sample prep and analytical platforms into a single, potentially portable system for point-of-care genotyping.</p> <p>This case study presents a model example of UVA students who make multiple decisions based on an that became a product and the basis for a Virginia company. Evan and Eric Edwards conceived of a greatly improved method for delivering epinephrine to those suffering from allergies and then spent over a decade learning how to get it on the market, finally succeeding in January 2013. Students will be asked to find their own solutions to the challenges that faced the inventors as they evolved their design and created a company; students then find out what the inventors did, and compare what actually happened to what they thought ought to have happened. From this case study, students learn lessons that better prepare them to be entrepreneurs.</p>	

This talk will describe Dr. Owen's role as a co-founder and CSO of the UVA Biotech Startup Company Setagon, Inc which was founded in 2001 and acquired by Medtronic Inc in 2007. He will describe the company's IP (production of drug delivery coatings and/or metallic devices), business plan, development and testing of our product (non-polymeric nanoporous coated drug eluting stents), marketing to potential buyers (stent companies), and the eventual acquisition by Medtronic. He will also describe interactions with Medtronic subsequent to the acquisition (through a new startup company NanoMed, Inc.) to achieve milestone payments. He will then have the class consider a series of discussion questions probing how you might have done things differently to achieve a more desirable outcome. [This lecture is an object lesson in biotech stepping stones and sinking sand and a do-not-miss event.]