

# **BIOENGINEERING IN THE BIOTECHNOLOGY AND PHARMACEUTICAL INDUSTRIES: FUNDAMENTAL AND REAL WORLD PERSPECTIVES**

**Course Number: 16:155:532 (CBE)  
16:125:575 (BME)**

**Index Number:73148 (CBE)  
70267 (BME)**

## **DESCRIPTION AND OBJECTIVES**

The goal of this course is to offer students insight into the practical aspects of industrial bioprocessing. Industrial practitioners from various fields of expertise provide lectures and facilitate discussions highlighting problems and issues that engineers and scientists encounter. Topics will vary from year to year but will include: drug discovery, drug metabolism, microbial fermentation and mammalian cell culture optimization and scale-up, monoclonal antibody, vaccine and gene therapy production, downstream purification, drug delivery, formulation, regenerative medicine, stem cell culture, tissue engineering, cellular therapies, regulatory considerations, manufacturing challenges, and clinical research. This course provides students with exposure to topics which are beyond the scope of a purely theoretically-structured course. After taking this course, students should have a better understanding of the challenges that engineers and scientists face in industrial bioprocessing.

## **COURSE DIRECTORS**

**Martin L. Yarmush, M.D., Ph.D., Professor, Department of Biomedical Engineering, Rutgers University; Director, Center for Engineering in Medicine, Massachusetts General Hospital**

Martin Yarmush received B.S. degrees in Biology and Chemistry from Yeshiva University, Ph.D. degrees in Biochemistry and Chemical Engineering from Rockefeller University and MIT, respectively, and an MD degree from Yale University. Dr. Yarmush has served on the faculties of MIT, Rutgers and Harvard leading research programs in the areas of Molecular and Cellular Bioengineering, Tissue Engineering, and Metabolic Engineering. He is currently a Professor in the Department of Biomedical Engineering at Rutgers and also leads the Center for Engineering in Medicine at the Massachusetts General Hospital. Dr. Yarmush is well known at Rutgers as the founding Director of the Biotechnology Training Program.

**Gregory Russotti, Ph.D., Director, Cellular Process Development, Celgene Cellular Therapeutics**

Gregory Russotti is currently the Director of Cellular Process Development at Celgene Cellular Therapeutics in Warren, NJ. His group is responsible for developing, optimizing, and scaling up cell isolation, expansion, and formulation processes and transferring these technologies to clinical and commercial GMP manufacturing facilities. Celgene Cellular Therapeutics isolates their cells from human placentas after full-term healthy births and plans to use these cells to treat a variety of unmet medical needs. Prior to joining Celgene in 2006, Greg spent nearly 15 years at Merck Research Laboratories developing products that included live virus vaccines, monoclonal antibodies, recombinant vaccines, and microbially-produced natural products. He worked on development and scale-up of cell culture, microbial fermentation, and downstream isolation processes and was responsible, at one point, for transferring processes into a pilot plant and, in

other roles, for transferring processes to manufacturing groups for clinical and commercial production, which included start-up of a new factory. Greg received his B.S. and M.S. degrees in Chemical Engineering from Rensselaer Polytechnic Institute. For his M.S. thesis he worked with Professor Georges Belfort on the design and construction of a novel perfusion mammalian cell bioreactor. Greg received his PhD in Chemical and Biochemical Engineering at Rutgers University while being supported by Merck's Doctoral Fellowship program. During his PhD studies, under the guidance of Professor Martin Yarmush, he investigated the concept of inducing cold tolerance in mammalian systems through prior stress conditioning, the ultimate goal of which was to design improvements in the ways we preserve cells, tissues, and organs.

**Bruno F. Marques, Ph.D., Senior Research Chemical Engineer, BioPurification Development, Bioprocess R&D, Merck Research Laboratories**

Bruno Marques earned a B.S. in Chemical Engineering (with Specialization in Energy/Environment/Economics) from the Illinois Institute of Technology, and a Ph.D. in Chemical Engineering from Carnegie Mellon University. During graduate studies, under the guidance of Prof. James Schneider, he developed di-alkyl peptide nucleic acid amphiphiles that can be incorporated into surfactant microstructures, such as liposomes and micelles, and serve as oligonucleotide sequence tags in highly sensitive analytical devices. In 2005, he accepted a position with Merck's BioProcess R&D group, where he has been working on downstream processing of therapeutic proteins, with an emphasis on development and scale-up of monoclonal antibody (MAB) purification processes. In this role, he has led tech transfer efforts from the bench-scale to Merck's pilot plants, for GMP production of MAB drug product for clinical trials. More recently, Bruno and his research team have been studying virus clearance during MAB purification, as well as the isolation of reverse chimeric (i.e. murine) MABs.

**TOPICS AND SPEAKERS, SPRING 2008**

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**Jan 23: (A) Introduction to Course Objectives and (B) Topics/Overview of Monoclonal Antibody Process Development**

Monoclonal antibodies (MABs) are an important and growing class of therapeutic proteins. There are currently 21 MABs on the market (and dozens more in clinical trials and at the research stage) with a wide variety of therapeutic indications. MAB process development and production methods will play a major role in the industry's ability to effectively bring this large number of products to the market rapidly and economically. This lecture will provide an overview of the various key elements of MAB production including: genetically engineering cell lines to produce high levels of MABs; designing nutritional media and optimizing bioreactor conditions that promote maximum cell growth and MAB production; scaling up bioreactor processes to pilot-scale and manufacturing-scale facilities; designing purification processes that maximize product yield while maintaining product quality; using bio-analytical methods to characterize key product attributes. After this lecture, students should understand the fundamentals of MAB process development and production, thereby preparing them for subsequent lectures in this field.

**Instructors: Gregory Russotti/Bruno Marques**

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**Jan 30: Mammalian Cell Culture Scale-Up for Monoclonal Antibody Production**

Scale-up of monoclonal antibody cell culture processes to the pilot-scale, for the production of clinical material, and to the manufacturing scale, for commercial manufacture, will be discussed. When scaling up these bioreactor processes, challenges include: avoiding cell damage; providing adequate mixing; satisfying cellular oxygen demand; removing carbon dioxide from the bioreactor; and minimizing foam accumulation in the bioreactor—All while maintaining sufficient cell growth and productivity. Students will learn about the various approaches to scaling up agitation and aeration parameters, as well as the advantages and disadvantages of each with respect to scale-up challenges.

**Instructor: Gregory Russotti**

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**Feb 6: PEGylation of Proteins—Modification of Pharmacokinetic Properties**

Although decisions about protein therapeutics are made primarily on the basis of biological activity, other properties such as pharmacokinetic behavior are critically important as well. This is especially true for relatively small protein therapeutics which may be cleared from the body too quickly to allow for effective therapy. One solution to this problem has been to attach a larger chemical moiety such as polyethylene glycol (PEG) to the protein to increase its half-life in circulation. The basis for this approach will be reviewed as well as how PEGylation fits in to a typical protein production process. In addition, other approaches to modifying the pharmacokinetics of proteins will be reviewed.

**Instructor: Eugene Schaefer, Sc.D., Director of Process Technology, Bristol-Myers Squibb**

Gene Schaefer received his B.S. degree in Chemical Engineering from Princeton University, and his M.S. and Sc.D. degrees in Biochemical Engineering from M.I.T. His M.S. thesis, supervised by Professor C. L. Cooney, investigated the production of the enzyme maltase by yeast, and his doctoral thesis, supervised by Professor D.I.C. Wang, focused on the production of a bio-surfactant. Gene worked for Genzyme for three years, in Boston and the UK, developing processes for a number of protein and carbohydrate products. He then led groups in several areas including purification, fermentation development and molecular & cell biology development, within the Biotechnology Development Group at Schering Plough for over thirteen years. Gene has held the position of Director of Process Technology at Bristol-Myers Squibb for the last six years.

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**Feb 13: Cell Line Development for Monoclonal Antibody Production**

Monoclonal antibodies (MAbs) represent a successful therapeutic area in terms of a growing number of products approved by the FDA and their clinical success. MAbs are produced by clonal cell lines and, as a result, the production of the cell lines themselves is a central process that will be the focus of this session.

The use of living cells as production factories has important implications unique to MAb production. Production of cell line begins with many millions of inherently genetically variable

potential host cells into which cDNAs encoding MABs are transfected. The diversity is further increased by variable transfection of the cells with significant consequences to their quality or performance. These include effects on growth rate and biomass potential, stability of expression, post-translation modification of MAb, and MAb yield, among other critical factors. The task in cell line production then becomes the isolation of those rare cells engineered such that all of these characteristics are optimized. Further, to ensure that a selected cell line performs as expected, the FDA enforces guidelines for cell line used in biologics production. These guidelines, as much as any technical issue in cell line production, need to be taken into account for a commercially viable outcome.

We will begin by discussing the most widely used and well established technologies for cell line production. Using these methods, it typically takes up to two years to obtain a cell line that may be scaled-up for the 10,000L production runs that are commonly used for sufficient yield. We will also cover some novel technologies developed to improve yield and/or timelines. This is a particularly timely discussion, as it happens that today's marketplace predicts rapid growth in the MAb biologics sector, forcing a juxtaposition of the benefits and risks of existing and novel technologies. Another force that may have a great and immediate influence is the potential legalization of generic biologics. Interestingly, one of the issues that complicates this discussion is establishing exactly how a generics producer could match every quality of the cell line used by the original brand-name producers, given all the complexities in cell line development. We will discuss which aspects of cell line production are relevant in this context and, if resolved, how the advent of generic biologics may have its own mark on which technologies may be favored.

**Instructor: Kambiz Shekdar, Ph.D., Chief Scientific Officer, Chromocell Corporation**

Kambiz Shekdar is a co-founder of Chromocell Corporation and has served as its Chief Scientific Officer since its inception in 2003. From 1992 to 1995, Kambiz attended Rutgers College where he received his B.A. in Biology. He was a Henry Rutgers Scholar in the Department of Biology at Rutgers College in 1995. From 1995 to 2003, Kambiz was a Graduate Fellow in the laboratory of Günter Blobel at The Rockefeller University in New York City where he obtained his Ph.D. His doctoral thesis work resulted in the biochemical purification and identification of a network of intra-nuclear fibers from rat liver nuclei which may represent a novel intra-nuclear transport or organizational scaffolding. During the course of this work, Kambiz had to create many stable cell lines. This normally required extensive manual tissue culture work and, as a result, Kambiz and Gunter co-invented a technology that automates cell engineering. At Chromocell, Kambiz has worked closely with CEO Christian Kopfli to establish the company. During the start-up phase, this included bench work in addition to coordination of the initial research program and collaboration projects. The company rapidly established itself and continues to grow at a fast pace; Kambiz currently oversees the scientific management of the various projects and scientifically contributes to corporate development of the company.

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**Feb 20: DNA Vaccines Product Development—From the Bench to the Clinic**

Vaccines have played a pivotal role in increasing life expectancy worldwide and, in particular, the developed world has seen life expectancy increase by over 30 years in the last century. Indeed, mortality from the nine major vaccine preventable diseases of the 19<sup>th</sup> century has

decreased by over 99.99%. While conventional vaccines (live, live-attenuated or inactivated) have held the predominant position amongst licensed products, they have often been plagued with manufacturing, potency, and safety issues making the search and development of newer vaccine platforms an attractive area for innovation. The key drivers being: ease of production, reduction in cost of goods, improving lot-to-lot consistency, stimulation of humoral and cellular immunity, improved efficacy, ease of delivery, better safety/toxicity profile, dose-sparing regimens, and rapid response strategies.

Plasmid DNA based vaccines and vaccines using viral vectors (adenovirus, MVA, and others) hold many of the attributes desirable in a vaccine candidate. While DNA-based vaccines have great potential, the best current DNA vaccines induce only weak cellular immunity in humans and are mainly being tested in the clinic as priming modalities that only weakly improve subsequent recombinant viral boosting. This lecture will focus on introducing students to the attributes that make DNA vaccines attractive for vaccine product development. We will start by discussing factors to consider while designing vectors, antigens and host strains. We will discuss current manufacturing processes for DNA and the peculiarities of DNA that makes process development and scale-up a challenge. We will touch upon the regulatory environment for DNA-based biologics. Lastly, we will discuss strategies to improve the immune potency of DNA vaccines and discuss cases that have generated widespread excitement (and controversy) in the community for the role of T-cell mediated vaccines.

**Instructor: Niranjan Y. Sardesai, Ph.D., Sr. Vice-President, Research & Development, VGX Pharmaceuticals, Inc.**

Niranjan Sardesai is currently the Senior Vice President of Research and Development at VGX Pharmaceuticals, headquartered in Blue Bell, PA. VGX is a clinical-stage biopharmaceutical company engaged in the development of novel drugs, and DNA-based vaccines and therapeutics, for major infectious diseases and cancer. Dr. Sardesai is responsible for formulating and directing the company's development strategy, as well as for directing the pre-clinical research programs. He also has direct oversight and P&L responsibility over the company's state-of-the-art cGMP manufacturing facility for plasmid DNA located in The Woodlands, TX. Previously, Dr. Sardesai served as VGX's Vice President of Product Development. He is an experienced veteran of the pharmaceutical industry, with a special focus on R&D and Management of Technology. Prior to VGX, Dr. Sardesai served as Founder and President of NVision Consulting Inc., a strategy consulting firm focused on entrepreneurial companies in the biopharma/life-science industry, and as Director of R&D at Fujirebio Diagnostics, Inc. At FDI, Dr. Sardesai oversaw all aspects of R&D activities and expansion of the oncology portfolio. He was responsible for establishing the R&D division following their acquisition from Centocor and for rebuilding the product pipeline. Products developed under his leadership include new-to-the-world diagnostic tests for mesothelioma (MESOMARK™), bladder cancer, and a multi-marker test for ovarian cancer. Dr. Sardesai also served as Senior Scientist at IGEN International, Inc., where his group helped develop a high-throughput screening platform for drug-discovery.

Dr. Sardesai received a Ph.D. in Chemistry from the California Institute of Technology, and an MBA in Entrepreneurship and Finance from the Wharton School of the University of Pennsylvania. He completed Fellowships at the Scripps Research Institute and at the

Massachusetts Institute of Technology. Dr. Sardesai received his M. Sc. in Chemistry (5-year Integrated Program) from the Indian Institute of Technology.

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**Feb 27: Large-Scale Bioreactor Design and Application**

Bioreactors are the most complex upstream bioprocess equipment item in the biotechnology and pharmaceutical manufacturing industries. They are the “factories” in which cultivation of cells to high densities permit the expression of useful proteins derived from recombinant DNA techniques. Drug companies that are in late stage phase III clinical trials or about to launch an FDA approved drug require facilities that can produce sufficient quantities of their product to meet market demands. A train of bioreactors having increasing vessel size is necessary for large scale production of modern therapeutic proteins, viruses, vaccines, monoclonal antibodies and a host of other biologically derived products in kilogram quantities. Scaling-up microbial fermentors and cell culture bioreactors can present challenges to the process and equipment designer. A thorough understanding of the inter-relationships between vessel geometry, aeration, agitation (mixing), oxygen transfer, and heat transfer are necessary to fully appreciate the scale-up methodology from laboratory to full-scale production. This lecture will explore OUR (Oxygen Uptake Requirements), agitator power needs, heat transfer demands, and aeration using air and / or oxygen. Control of critical parameters will be discussed as they relate to the real time measurement of gas flows, pressure, temperature, agitator speed, pH, DO (Dissolved Oxygen), and off-line measurements.

**Instructor: Ernest L. Stadler, P.E., Director Custom BioProcess Systems, Sartorius Stedim Biotech**

Ernest L. Stadler is Director of Custom Bioprocess Systems at Sartorius Stedim Biotech, a manufacturer of fermentors, bioreactors, automation software / hardware, and other related bioprocess laboratory and custom large scale equipment. A member of ASME, ISPE, and PDA, Mr. Stadler is a registered Professional Engineer in PA and NJ, holding a BS in Mechanical Engineering from NJIT and has done graduate studies at Lehigh University in biotechnology. Mr. Stadler has broad based expertise in automation, process and mechanical design for a wide range of Bioprocess equipment having served the biotechnology industry for over 19 years. He is a frequent speaker, teacher, and workshop leader on the design and application of fermentors and bioreactors, particularly relating to biotechnology process scale-up and optimizing performance. Ernest served as Course Director, Lecturer and Workshop Leader for over 12 years with the ASME BioProcessing Technology Seminar series. He has authored articles and papers and was awarded the 1998 Article of the Year by Pharmaceutical Engineering Magazine, a publication of the ISPE. He has served the past 3 years on the Board of Directors for the SBP being a founding member and is the current SBP Treasurer. Mr. Stadler can be reached via email at [ernest.stadler@sartorius.com](mailto:ernest.stadler@sartorius.com)

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**Mar 5: Recovery Process Development and Validation for a Therapeutic Monoclonal Antibody**

Monoclonal antibodies (MAb) represent the largest class of protein therapeutics in the biotechnology industry. While all MAbs share many characteristics, each MAb has a unique combination of biochemical properties that can be exploited or that must be overcome for

purification. Successful development of a MAb purification process also requires consideration of product quality, economics, manufacturing constraints, regulatory and product safety issues, and speed of development. These factors must be continually evaluated as the process is transferred to a pilot manufacturing facility and, ultimately, to a commercial manufacturing facility. Prior to obtaining a license to launch the MAb commercially, a process validation package must be prepared to demonstrate that the manufacturing process will consistently perform as the manufacturer claims. Process development, and validation strategies and alternatives will be discussed using illustrative examples.

**Instructor: William K. Wang, Ph.D., Director, Process Biochemistry, MedImmune**

William K. Wang is currently Director, Process Biochemistry at MedImmune, a biopharmaceutical company in Gaithersburg, MD. Bill leads a team of scientists and engineers responsible for process development, technology transfer, and clinical and commercial manufacturing support. Prior to joining MedImmune in 2007, Bill supported purification and filling operations, and process transfer for therapeutic proteins at Biogen Idec's Cambridge, MA commercial and clinical manufacturing facility. Prior to joining Biogen Idec in 2002, Bill developed and transferred purification processes for clinical manufacturing of therapeutic proteins at GlaxoSmithKline. He completed his M.S. and Ph.D. in Chemical Engineering from the University of Rochester. His doctoral research focused on the cloning and expression of the gene coding for a *Clostridium thermocellum* cellulase. Bill completed his B.S.E. in Chemical Engineering at the University of Pennsylvania. He was the editor of the book, *Membrane Separations in Biotechnology: Second Edition, Revised and Expanded* and is an author on over 25 articles, chapters, or abstracts for presentations. Recently, he was a Program Chair for the Division of Biochemical Technology at the 2007 ACS National Meeting.

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**Mar 12: Live Virus Vaccine Process Development**

Viral vaccines are an important class of therapeutics in the pharmaceutical industry. A production challenge in live virus vaccine manufacturing is the large-scale cultivation of viruses. Viruses, by themselves, are non-replicating organisms and, therefore, need a host in order to replicate. Typical hosts include *in vivo*, *in ovo* (egg cultivation), and *in vitro* systems. Primary cells were the traditional cell type for *in vitro* systems but, more recently, human diploid cells and continuous mammalian cell lines have been developed for viral cultivation. The cells used in these *in vitro* systems are anchorage-dependent; that is, they require an attachment surface in order to grow. Various cell culture configurations for anchorage-dependent cells will be compared, and the advantages and disadvantages of these configurations—with respect to scale-up, economics, process robustness and control—will be discussed.

**Instructor: Gregory Russotti**

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**Mar 26: Technology Transfer of a Biological Product from R&D to Manufacturing**

As a biological or pharmaceutical product moves through a company's pipeline, it will undergo process development, scale-up, and testing through Phase I and Phase II clinical trials. If the product proves successful from a clinical stand-point, the financial feasibility of manufacturing the product on full-scale will be evaluated by the company. Factors such as manufacturing

location, manufacturing costs, expected time to licensure, and current anticipated sales, will factor into the *Net Present Value (NPV)* assigned to the product. Based on proven clinical results and a positive NPV, the process technology will be transferred into manufacturing in preparation for Phase III clinical trials and product licensure. The steps associated with a successful technology transfer will be discussed, including facility design fundamentals and start-up, process demonstration, and product licensure.

**Instructor: Kimberly Dezura, Director, Viral Vaccine Technology & Engineering, Merck Manufacturing Division**

Kim Dezura is currently the Director of Viral Vaccine Technology & Engineering within the Merck Manufacturing Division. Her group provides technical support for four live virus vaccine areas (both licensed and new products). Within this group, she has supported both licensed vaccine processes as well as the transfer of new vaccine products into MMD. As part of technology transfer efforts, Kim has had exposure to the design, construction, qualification, and start-up of a biological manufacturing facility and its associated processes. Kim Dezura received her B.S. and M.S. degrees in Chemical Engineering from the University of Pittsburgh. For her M.S. thesis, she worked with Dr. Mohammed Ataai in the expression of IL-1 receptor antagonist protein using the lapine synovial cell line HIG-82 in a bioreactor setting. This research was a joint effort between the Chemical Engineering department and Orthopedics, in the School of Medicine, in support of rheumatoid arthritis treatment.

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**Apr 2: Technology Evaluation and Process Development Strategy for the Production of Therapeutic Proteins**

This session will address the available technologies for the large-scale production of biopharmaceuticals. The relatively high approval rate for high-demand and high-dose biological products has raised concerns regarding production capacity, reliability on the production technology, and the economics for this type of product. This class will review current literature on process scale-up and technology assessment. The class will focus on the strategy used to reconcile process development timelines and appropriate production scale, with the uncertainties associated with product development and investments required to support it.

**Instructor: Marco A. Cacciuttolo, Ph.D., President and CEO, PERCIVIA LLC.**

Dr. Cacciuttolo is the Chief Executive Officer of PERCIVIA LLC, the PER.C6 Development Center located in Cambridge, Massachusetts. This center is a joint venture between Crucell, B.V. and DSM Biologics, B.V. Previously, Dr. Cacciuttolo was Vice President of Technical Operations at Medarex, Inc., a biotechnology company with headquarters in Princeton, New Jersey. In that role, Dr. Cacciuttolo was responsible for process development, analytical sciences, quality control, GMP manufacturing, validation, materials management, and the management of outsourcing activities. Dr. Cacciuttolo was previously Manager, Cell Culture Manufacturing at MedImmune, Inc., Frederick, Maryland. In this role, Dr. Cacciuttolo was responsible for the manufacturing of Synagis, the first approved monoclonal antibody against an infectious agent. He also participated in the commissioning and licensure of the facility to manufacture Synagis. Prior to this assignment, Dr. Cacciuttolo was a process development engineer in Cell Culture Development at MedImmune, Inc., Gaithersburg, Maryland. Dr.

Cacciuttolo received his Ph.D. in Biochemical Engineering from the University of Maryland, Baltimore County and his B.S. in Biochemical Engineering from the Catholic University at Valparaiso, Chile.

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**Apr 9: Challenges and Strategies in Cell Therapy and Tissue Engineering Bioprocess Development**

When living cells are used as therapeutics, the challenges of meeting FDA safety, efficacy and manufacturing standards are amplified by the inherent variability of the product. The additional challenges posed by process and distribution economics have kept the number of such therapeutics that reach wide clinical distribution quite small. Notwithstanding these obstacles, the great promise of this field as a component of the new clinical paradigm of regenerative medicine has stimulated continuing efforts to bring new such medical devices into clinical trials.

This session will focus on cell based therapies that rely on normal cells recovered from human tissues. The emphasis will be on practical approaches to address FDA issues, from tissue procurement through cell line and final product characterization; and process economics issues, from pilot scale through commercial launch. A case study will be included, of the product OrCel<sup>®</sup>, produced by Forticell Bioscience (formerly Ortec International). OrCel<sup>®</sup> is a tissue engineered skin substitute in the form of a cryo-preserved bilayered cellular matrix in which normal human donor epidermal keratinocytes and dermal fibroblasts are cultured. Forticell entered into an agreement with a contract manufacturer for the late stage clinical trial supply and commercial manufacture of OrCel<sup>®</sup>. The ensuing technology transfer and production scale up will be discussed.

**Instructor: Melvin Silberklang, Ph.D., Chief Scientific Officer and Vice President, Research and Development, Forticell Bioscience**

Mel Silberklang is currently Chief Scientific Officer and Vice President of Research and Development at Forticell Bioscience (formerly known as Ortec International). He has over 26 years of experience in the Pharmaceutical (Merck Research Laboratories, 1981-1993) and Biotechnology (Enzon, Inc., 1993-1995; Ortec International, Inc., 1995-2007) industries and two years of prior academic experience on the research faculty of the University of California at San Francisco. His background in biotechnology is very broad, spanning the gamut from discovery research through product development and production. He has worked on: gene cloning and synthesis; protein and antibody engineering; high-level animal cell expression; live and subunit viral vaccine development and production; primary cell and stem cell isolation, characterization and culture; process scale-up and development and GMP production of proteins, monoclonal antibodies, vaccines, cell therapies, stem cell therapies, tissue-engineered three-dimensional tissue-like cell cultures, biomaterial matrices and scaffolds. Since assuming the position of Vice President for Research and Development at Ortec (1996), he has been involved in every step of a tissue engineering project to develop a cultured, bi-layered cellular matrix as a wound healing product, trademarked OrCel<sup>®</sup>. The program spans: high-grade (bovine) collagen procurement, testing, and processing; human tissue (foreskin) procurement and processing; primary skin cell line establishment, expansion, cryo-preservation, safety and efficacy testing; final product process development, technology transfer, production, Quality Control, packaging, cryo-

preservation and shipment. The OrCel<sup>®</sup> product has gotten two FDA approvals and is presently undergoing FDA PMA review of an advanced cryo-preserved form. Dr. Silberklang is presently also directing research into optimization of autologous adult stem cell isolation, characterization, expansion, differentiation, and therapeutic delivery using natural and synthetic biomaterial matrices.

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**Apr 16: Standard Oil and the Vertically Integrated Pharma Model: Repeating History**

In 1911, the U.S. government broke up Standard Oil, citing its monopoly position in all aspects of energy production ("vertically integrated," from exploring/drilling to retail delivery of product). In a similar action, AT&T (responsible for everything from handset production to undersea cable maintenance) was broken up in 1984. In both cases, a credible argument can be made for a wave of innovation and value-creation following on the heels of the break-ups. The pharmaceutical industry has been traditionally vertically integrated, with only the clinical trial aspects obligatorily contracted out. Big Pharma, perhaps inspired in the 1980s by the hope that genomics would provide a "unified field" approach to human health, began a further consolidation, leading to the mega-companies of today. With genomics, and other expensive front-end technologies, including high-throughput screening, it seemed to make sense to grow, amortizing these costs over a larger base.

While it is unclear that these changes causally lead to the current "innovation crisis," Pharma has recently started to shift business models, moving away from vertical integration towards a model of "open innovation." This has implications for all aspects of the business, and the science and technology it supports. We will discuss the underlying observations, and the implications for employment in the industry. Also to be considered is outsourcing, a.k.a. the "Asia Model."

**Instructor: Robert A. Zivin, Ph.D., Corporate Director, Johnson & Johnson Corporate Office of Science and Technology**

Bob Zivin received his B.S. in Biology at Northern Illinois University and his Ph.D. in Microbiology at the University of Chicago. His thesis work was directed toward the molecular genetic characterization of an atypical bacteriophage. After a post-doc at the National Cancer Institute, Bob spent several years at the Merck Research Laboratories in West Point, PA, working on the cloning and bacterial production of therapeutic peptides. Bob has spent over eighteen years with Johnson & Johnson where, among other responsibilities, he led the Antibody Humanization effort at the R.W. Johnson Pharmaceutical Research Institute. In 1995, Bob established and headed the Department of Exploratory Technology at RWJ PRI (now J&J Pharmaceutical Research and Development, L.L.C.), working on the application of new technologies to the drug discovery process. Since November 2003, he has been a member of the J&J Corporate Office of Science and Technology.

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**Apr 23: Cellular Therapeutics: Accomplishments, Promises, and Challenges**

There has been limited but successful use of cells in medicine, and there is great promise for additional cell-based therapeutic applications. Numerous challenges related to medicine and

biology, safety/regulatory, manufacturing, and business must be overcome during further development of cell therapies. As the ability to address these issues hinges on all aspects of design, the bioengineering of a product is critical to its success. This session will focus on the current state of the cell therapy field, and engineering approaches to dealing with challenges. Among the challenges that will be discussed are cell sourcing, matching, scale-up, cell banking, testing, and storage. This lecture will also provide an overview of developments at some notable companies pursuing cell therapies.

**Instructor: Thomas A. Brieva, Ph.D., Senior Research Scientist, Cellular Process Development, Celgene Cellular Therapeutics**

Tom Brieva received a B.S. in Chemical Engineering and a B.A. in Biological Sciences from Rutgers University. His Ph.D., also from Rutgers, combined Chemical Engineering and Cell and Developmental Biology in an Interdisciplinary Ph.D. program aimed at training useful for Tissue Engineering. His Ph.D. research involved engineering hepatocyte growth and function via cell-cell adhesion receptors under the direction of Dr. Prabhas Moghe. Tom also completed two NIH-sponsored training programs: the Biotechnology Training Program and the Molecular Biophysics Training Program. Following post-doctoral research on cell targeted nanocarrier-based drug delivery in Dr. Joachim Kohn's lab at the NJ Center for Biomaterials at Rutgers, Tom began his current tenure at Celgene. He presently pursues processes for the isolation, expansion, and formulation of therapeutic placental stem cells in a safe, robust, reproducible, controlled, and cost-effective manner. Collectively, Tom's work throughout his career has focused on engineering cells via culture processes, cues, or small molecules.

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**Apr 30:           Development and Commercialization of a Regenerative Tissue Matrix for Soft Tissue Repair and Replacement**

Regenerative Medicine is a relatively new field that encompasses the disciplines of cell biology, extra cellular matrix biochemistry, bioengineering, transplantation, immunology, and tissue engineering, all focused on harnessing and directing the body to regenerate new tissues and organs. A number of approaches are under investigation in many academic and industry programs and include: Replacement of tissue with entirely synthetic materials constructed *ex vivo*; Functional restoration with constructs that comprise both synthetic and cellular components; Scaffolds that revitalize in vivo and transition to normal tissue; Combinations of temporary scaffolds (natural or synthetic) with cellular components; and Cellular therapies, including stem cells and genetically modified cells. At LifeCell Corporation we have developed and commercialized extra cellular matrix-based products for soft tissue repair and reconstruction. The key to success of the technology has been driven by recognition of the importance of preserving the native structure and composition of the extra cellular matrix. When implanted in the body, the intact scaffold is rapidly vascularized and populated by host cells with minimal signs of inflammation. Positive recognition by the body is key to remodeling to native tissue and long term efficacy; and clearly distinguishes this material from other biologic or synthetic materials that elicit immune rejection and subsequent resorption or encapsulation. Development of an intact, sterile, regenerative tissue matrix derived from an animal source will be described. This will include procurement from a controlled animal herd, processing methods that will scale to meet demand, overcoming graft rejection in animal to human xeno-transplantation, long-term room temperature preservation of a complex biologic, sterilization without degrading or cross

linking extra cellular matrix components, and regulatory considerations in choosing the product development path. The preservation of key matrix components was verified by *in vitro* and *in vivo* testing, and efficacy assessed by evaluation in a number of animal models including non-human primates. The pathway to final clearance by the FDA as a 510(k) medical device will be described, as well as early clinical evaluation in hernia repair and post-mastectomy breast reconstruction. This lecture will touch on the multidisciplinary approach required to successfully address unmet needs in regenerative medicine, encompassing tissue structure and function, immunology of transplantation, identification and development of appropriate animal models, and issues related to regulatory requirements in developing a medical device.

**Instructor: David J. McQuillan, Ph.D., Vice-President Research, LifeCell Corporation**

David McQuillan is Vice-President for Research at LifeCell Corporation and has been in that position since 2002. From 2000 to 2002 he was Director of Research at LifeCell. Prior to LifeCell, David spent 20 years in academia studying extra cellular matrix biology, the role in biosynthesis of orthopedic tissues, structure and function of extra cellular proteoglycans and collagens, and the role in wound healing and tissue repair. David received his BSc and PhD degrees from Monash University, Australia in Connective Tissue Research. He did postdoctoral work at the National Institute of Dental Research at NIH from 1985-1989, studying carbohydrate chemistry. He was a NH&MRC Research Fellow in the Orthopedic Research Unit, University of Melbourne 1990-1994, studying heritable diseases of connective tissue metabolism and studying interactions of matrix molecules by over-expression of recombinant glycoproteins. In 1994 David was recruited to the Institute of Biosciences and Technology, Texas A&M University where he managed an NIH-funded program studying the function of extra cellular matrix molecules.

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