

## **MOLECULAR MEDICINE IRELAND COURSES & WORKSHOPS**

### **MOLECULES TO MEDICINES: HOW BIOPHARMA DELIVERS Lecture Course**

Wednesday 15 October 2008; 0930-1730

Venue: Durkan Lecture Theatre, TCD Institute of Molecular Medicine, St James's Hospital

This MMI/Wyeth Course will be of interest to research students, academic staff and clinicians, whether contemplating a career in industry or doing translational research in academia. The lectures provide an overview of biopharmaceutical discovery, development and manufacturing, delivered by key staff from Wyeth Pharmaceuticals. A clinical perspective is provided by academic clinician scientists.

#### **LECTURE COURSE: Wed 15 October; 0930-1730**

0930 **Overview**

#### **MOLECULES TO MEDICINES: CLINICAL PERSPECTIVE**

*Session Chair: Prof Joseph Keane, (St James's hospital & Institute of Molecular Medicine, TCD)*

#### 0940 **The role of biopharmaceuticals in the treatment of rheumatoid arthritis**

Dr Donough Howard (St James's hospital)

#### 1000 **Pulmonary fibrosis**

Professor Michael P. Keane (St Vincent's University Hospital & UCD)

#### 1020 **Receptor tyrosine kinase inhibitors: the hunt for the cancer "wonder drug"**

Dr Dearbhaile Collins (Beaumont Hospital & RCSI)

**DISCOVERY** Dr Davinder Gill (Assistant Vice President, Biologic Therapeutics, Wyeth Pharmaceuticals, Cambridge, MA, USA)

#### 1040 **Introduction to the business of discovering biopharmaceuticals**

1125 **Coffee/Tea**

1145 **Current biopharmaceutical product candidates and a look into next generation Technologies**

**DEVELOPMENT** Dr Patrick Gammell (Wyeth Biotech)

#### 1230 **Cell line development**

1315 **Lunch break (lunch will be provided)**

1400 **Process development**

**MANUFACTURING** Dr Paul Dillon (Wyeth Biotech)

#### 1445 **Introduction to the science and technology of biopharmaceutical manufacturing**

1530 **Coffee/Tea**

1550 **Focus on the application of molecular technologies in manufacturing environments**

#### 1630 **Evolution of a Science Based Approach for Regulatory Approval of Complex Biological Therapeutics**

Dr. Kenneth B. Seamon (Institute of Biotechnology, University of Cambridge)

1710 **Discussion & round up**

## Abstracts

### **Pulmonary Fibrosis**

**Prof Michael Keane** (St Vincent's University Hospital & UCD)

Fibroproliferation in the lung is a key component of a variety of lung diseases, particularly interstitial lung disease, and is an important cause of morbidity and mortality. The mechanisms that regulate fibroproliferation in the lung are poorly understood and consequently the therapeutic options have been extremely limited. Recently there has been renewed interest in the development of new therapeutic options for patients with pulmonary fibrosis. There have been several large clinical trials that have either been completed or are ongoing that are directly testing therapies that have arisen from basic investigations on the mechanisms of pulmonary fibrosis. This presentation will give an overview of the current understanding of the mechanisms of pulmonary fibrosis and how this has been translated into clinical trials of novel treatments.

### **Receptor tyrosine kinase inhibitors: the hunt for the cancer “wonder drug”**

**Dr Dearbhaile Collins** (Beaumont Hospital & RCSI)

In the last twenty years, there have been many exciting discoveries of novel biopharmaceutical therapies against the receptor tyrosine kinases (RTKs). Breast cancers that overexpress these RTKs, particularly HER2, have been significantly associated with poor patient survival, increased rate of tumour recurrence and metastasis as well as tumour resistance to radio- and chemotherapy. This presentation intends to introduce the predominant competitors in RTK inhibition such as trastuzumab (Herceptin), lapatinib (Tykerb), gefitinib (Iressa), erlotinib (Tarceva) and pertuzumab (Omnitarg). The lecture will divulge the molecular mechanisms by which they each act, the reasons for tumour resistance to these therapies, their success in translating from the laboratory to clinical trials and their future roles in the treatment of breast cancer.

### **Introduction to the business of discovering biopharmaceuticals**

#### **Current biopharmaceutical product candidates and a look into next generation technologies**

**Dr Davinder Gill** (Assistant Vice President, Biologic Therapeutics, Wyeth Pharmaceuticals)

The Biotech industry was launched in 1982 when the US Food and Drug Administration approved Humulin, a recombinant form of human insulin genetically-engineered to be produced in *E. coli*. From humble beginnings less than 25 years ago, the Biotech industry has expanded steadily over the years with over 80 recombinant DNA products approved by the FDA to date. Today, the collection of Biotech products includes secreted factors, fusion proteins, monoclonal antibodies and other products.

The Pharmaceutical industry, working in close collaboration with academic institutions, research organizations and medical centers, has developed advanced tools and technologies to enable Biotech drug discovery. These technologies involve molecular and cellular biology techniques, protein structure/function technologies, protein engineering, in vitro assays and animal models. This session will describe how the Pharmaceutical industry adapts such diverse tools to the discovery of biotech drugs, how projects are shepherded through the complexity of pharmaceutical product development, how scientific innovation and creativity are utilized and how the risk of drug discovery is spread over multi-pronged strategies.

#### **Suggested Reading**

Walsh, G. (2003). Biopharmaceutical benchmarks – 2003. *Nat. Biotechnol.* 21, 865-870. [PubMed Entry](#)

Gill, D.S. and Damle, N.K. (2006). Biopharmaceutical drug discovery using novel protein scaffolds. *Curr Opin Biotechnol.* 6, 653-658. [PubMed Entry](#)

### **Manufacturing cell line development**

#### **Process development and characterization**

**Dr Patrick Gammell** (Scientist at Wyeth Biotech)

The Biotechnology industry has changed dramatically since the first FDA approval for insulin in 1982. The earliest recombinant protein products, including insulin, growth hormone and coagulation factor VIII, were replacements for naturally-occurring endogenous human proteins that were already available as existing products from alternative sources, including human pituitaries and plasma. The technologies used for the production of these early products leveraged heavily off the available “academic” expression platforms (host cells, vectors and media formulations) and the high potency of many of these early products (hormones, growth factors and enzymes), enabled relatively low-yielding process to be commercially viable. The past 20-

years has seen much change in the types of biotechnology products being made and a trend towards high-dose chronic administration, particularly for antagonist antibody products. As a result, the biotechnology manufacturing process has undergone considerable “industrialization” with a drive towards significantly improved expression levels, process yields and ease of product administration, with shorter process development timelines. In addition, much effort and attention has been paid to improving the quality of production process, particularly with regard to product consistency and viral/TSE safety – a significant improvement over the early human tissue – and plasma-derived products. This session will describe the major elements and considerations in the development of a typical manufacturing process and highlight some of the current and future challenges.

#### **Suggested Reading**

Kelley, B.D. (2001). Bioprocessing of therapeutic proteins. *Curr. Opin. Biotech.* 12, 173-174 [PubMed Entry](#)

Wurm, F.M. (2004). Production of recombinant protein therapeutics in cultivated mammalian cells. *Nat. Biotechnol.* 22, 1393-1398 [PubMed Entry](#)

Therapeutic Proteins, Methods and Protocols (2005). Smales, C.M. and James, D.C., Eds. Humana Press.

### **Introduction to the science and technology of biopharmaceutical manufacturing**

**Dr Paul Dillon** (Wyeth Biotech)

The contribution of biopharmaceuticals to medicine has grown rapidly from an early start as complex mixtures of protein preparations extracted from tissue to today’s highly purified proteins produced from cell culture. Early biopharmaceuticals were often replacement proteins such as cytokines or growth factors that were used to supplement a deficiency that contributed to the disease process. The recombinant proteins in use today have a variety of modes of action and are used to tackle a wide range of diseases. The proteins available now are often specifically targeted against identified proteins in the circulatory system and impact disease by binding molecules such as mediators of inflammation or by marking tumour cells for destruction. Together with a major impact on a number of serious disease states, these new medicinal products have had significant commercial success with sales of non-vaccine biopharmaceuticals exceeding €37BN in 2004. This new generation of medicines has been enabled by breakthroughs in a number of areas in science and technology. Apart from the huge explosion of knowledge in biology which has revolutionized the Discovery and Development processes, advances in cell culture technology, bioprocess technology and protein characterization have provided the platforms on which stable, reliable and economical manufacturing systems have been established.

The course will introduce participants to the biotechnology industry and review its recent history. This session will present an overview of biopharmaceutical manufacturing and discuss facility design and operation in outline. The participants will see how the various technologies operate in the plant and how they are used in the various unit operations as well as in the supporting functions such as technical support and analytical laboratories. The course will also examine the interrelationships on a manufacturing site and look at how the process of manufacturing a batch involves a wide range of participants.

#### **Focus on the application of molecular technologies in manufacturing environments**

A unique feature of the production of biopharmaceuticals, distinct from medicines produced by chemical synthesis, is the use of living cells as the primary unit of production of the active ingredient. This feature and the relative complexity of the molecules produced by living organisms creates a need and an opportunity to utilize modern molecular techniques in the operation and control of biopharmaceutical processes. In the upstream area of the process, where cell growth and protein production occurs, a sound understanding of cell biology and physiology allows scientists and engineers to monitor and control the growth of cells and manage their production of recombinant proteins.

Building on the work carried out by Development colleagues, manufacturing technologists carefully manage bioreactor processes to ensure optimal conditions for growth and protein purification. Later, in the downstream area, where the protein is captured and purified, a sound knowledge of the physicochemical characteristics ensure that conditions here are similarly managed to maintain maximum output and quality. All of the critical processes in a plant manufacturing biopharmaceuticals should be validated, usually operated under significant automated control and should not require frequent intervention. However, natural variability can occur in biological systems and the investigative scientists who support the plant will utilize a range of modern technologies to solve problems in routine manufacturing or to support planned changes. This course will outline some of the approaches that are taken and use a number of case studies to show how this work is carried out.

### **Suggested Reading**

Walsh, G. (2003). Biopharmaceutical benchmarks – 2003, *Nat. Biotechnol.* 21, 865-870. [PubMed Entry](#)

### **Evolution of a Science Based Approach for Regulatory Approval of Complex Biological Therapeutics**

[Dr Ken Seamon](#) (University of Cambridge, Department of Chemical Engineering and Biotechnology)

Biological therapeutic products produced using recombinant DNA technologies have benefited over 300 million patients over the past twenty years. The technology utilized in the production of these technologies as well as the therapeutic targets for their use has evolved significantly. This has necessitated a regulatory system that can accommodate the complexities of these proteins with regard to their structure, their manufacturing, and their biological activities. The regulatory system used for the evaluation of these products has continued to evolve along with the products and has always maintained a flexible approach that can accommodate novel therapies and technologies. This talk will provide an overview of the origins of biological therapeutic regulation and present a number of key examples that illustrate the complexities in regulating products developed with new technologies.

### **Instructor Biographies:**

#### **Dr Dearbhaile Collins** (Beaumont hospital & RCSI)

Dr Dearbhaile Collins (Beaumont Hospital & RCSI) qualified from UCD Medical School in 2003 and commenced a career in General Surgery, with a particular interest in breast surgery. She is currently pursuing a PhD on the molecular mechanisms of breast cancer resistance to both conventional hormonal therapies and the tyrosine kinase receptor inhibitor, Herceptin. Her work has uncovered novel methods by which breast tumours adapt to the inhibitory effects of Herceptin. Her research to date has earned her the prestigious Patey Prize award at the Society of Academic and Research Surgeons (SARS) in the UK this year, the 2008 Joint Research Fellowship of the Royal Colleges of Surgeons in Ireland and England and numerous national and international presentations.

#### **Prof Michael Keane** (St Vincent's University Hospital and UCD)

Michael Keane is Professor of Medicine and Therapeutics at UCD and Consultant Respiratory Physician at St Vincent's University Hospital. He graduated from UCD in 1989 and following initial clinical training in Dublin moved to The University of Michigan, Ann Arbor for a fellowship in pulmonary and critical care medicine in 1995. He subsequently took up a faculty position at University of Michigan in 1998. In 2000 he moved to UCLA where he remained until 2007 when he returned to Dublin. He has an interest the basic investigation and treatment of inflammatory lung diseases and particularly pulmonary fibrosis.

#### **Dr Davinder Gill** (Wyeth Pharmaceuticals)

Davinder Gill is Assistant Vice President, Biologic Therapeutics at Wyeth Research in Cambridge, Massachusetts. Davinder got his Bachelor's degree in Chemical Engineering at the Indian Institute of Technology and a PhD also in Chemical Engineering from the University of Houston, Texas. Davinder was a Cancer Research Institute postdoctoral fellow at Massachusetts General Hospital/Harvard Medical School. Prior to Wyeth, Davinder spent several years at Millennium Pharmaceuticals in their Biotherapeutics Division advancing a number of protein therapeutics in Oncology and Inflammation.

**Dr Paul Dillon** (Wyeth Biotech, Grange Castle, Ireland)

Paul Dillon is a Senior Scientist in the Analytical Development Team at Wyeth Biotech (Wyeth Medica Ireland) and has six years experience in the biotechnology industry. Paul has a Biology degree from Maynooth University (Ireland) and holds a PhD in Applied Biochemistry from Dublin City University. Paul's role is to support method development (qualification and validation), process and protein characterisation for therapeutic proteins. Prior to joining Wyeth, Paul worked as a postdoctoral fellow at Dublin City University in the development of molecular technologies to generate single chain antibody fragments. Paul has published original and applied research in many peer-reviewed journals including Proc Natl Acad Sci, Journal of Immunological Methods and Biosensors and Bioelectronics.

**Dr Patrick Gammell** (Wyeth Biotech, Grange Castle, Ireland)

Patrick Gammell is a process development scientist at Wyeth Biotech. Patrick has a BSc Biotechnology degree from Dublin City University (Ireland) and holds a PhD in Biotechnology also from Dublin City University. Within Wyeth Patrick is involved in the development, scale-up and validation of cell culture processes for the manufacture of therapeutic proteins. Prior to joining Wyeth Patrick was a senior research scientist at the NICB in Dublin City University where he was coordinator of a project team in an SFI-funded collaboration with Wyeth scientists in Massachusetts and Ireland to investigate cell line properties that result in improved production-related phenotypes. Prior to that Patrick was a post doctoral scientist investigating IGF-1 signaling in NUI Cork. Patrick has 4 patents relating to molecular profiles of CHO cells that relate to productivity and growth related phenotypes and has also published original and applied research in a number of biotechnology based journals including Proteomics, the Journal of Biotechnology, Biotechnology Progress, Molecular Biotechnology, BMC Biotechnology, Cytotechnology and the Journal of Endocrinology.

**Dr Ken Seamon**, (University of Cambridge, Department of Chemical Engineering and Biotechnology, Masters in Bioscience Enterprise)

Dr Ken Seamon brings a wealth of experience of USA and European biotech, and currently teaches on the MBE programme course at the University of Cambridge, UK. Dr Seamon was until recently Vice President, Regulatory Affairs at Amgen Corporation, London, with responsibility for the Regulatory CMC Group and interactions with operations, as well as for developing policy for Follow on Biologics and Biosimilars. Prior to this Dr Seamon was Senior Vice President, Drug Development at Immunex Corporation, Seattle, Washington State. Earlier in his career Dr Seamon spent 13 years with the Food and Drug Administration (FDA), and served latterly as the Director of the Office of Therapeutics Research and Review and Associate Director for Research at the Center for Biologics Research and Review at Bethesda, Maryland.