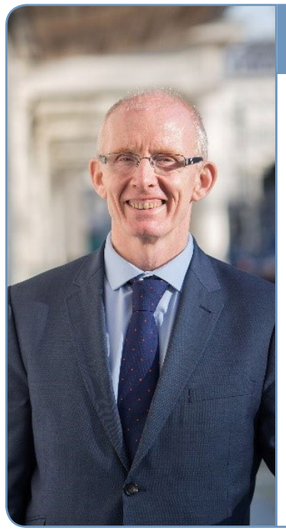
LIQUID PHASE OLIGONUCLEOTIDE SYNTHESIS



ANDREW LIVINGSTON, Professor of Chemical Engineering,
Queen Mary University of London

Andrew Livingston studied Chemical Engineering and then worked at an NZ food processing company followed by a PhD at Cambridge UK, and in 1990 joined the Department of Chemical Engineering at Imperial College, serving as HoD 2008-2016. He has recently taken up a new post as Vice Principal Research and Innovation at Queen Mary, University of London. He leads a research group with interests in membranes for molecular separations in liquids and the development of chemical processes using these membranes. Awards include the Junior Moulton Medal, Cremer and Warner Medal, and Underwood Medal of IChemE, and Silver Medal of Royal Academy of Engineering. AGL was elected a Fellow of the Royal Academy of Engineering in 2006. In 1996, AGL founded Membrane Extraction Technology, a start-up which developed solvent stable Organic Solvent Nanofiltration (OSN) membranes was acquired by Evonik Industries of Essen, Germany. In 2018 AGL founded Exactmer, a new start-up dedicated to the production of exact polymer molecules including oligonucleotides, peptides and synthetic polymers such as PEG, using Nanostar Sieving technology.

The oligonucleotides market has seen growth recently thanks to the advancements in synthesis technologies, increased use of oligos as therapeutics and improved manufacturing techniques. The market is gaining more and more attention from both pharmaceutical & biotech companies as well as academic & research institutions.

Prior to our 7th Annual Peptides & Oligonucleotides Congress, we sat down with one of our highly esteemed speakers, Andrew Livingston, Professor of Chemical Engineering, Queen Mary University of London to discuss the interesting work he is conducting.

The market for oligonucleotides has seen growth since 2013, which many consider as a big year for them. In your opinion, what are the key factors driving the market's growth?

Oligonucleotide therapies offer a completely new therapeutic modality, through manipulation of gene expression, allowing for the development of therapeutics which affect protein targets that cannot be effectively treated by small-molecule or protein therapeutics. By interfering with protein expression at the RNA level, specific malfunctioning genes can be targeted, manipulated, silenced and/or modulated. Further, immune system modifications may offer treatment for a multitude of autoimmune disorders that are in many cases extremely challenging to treat with currently available drugs. Finally, because RNA and DNA strands are essentially combinations of 4 repeated nucleic acid bases, and so have a combinatorial nature, oligonucleotide pharmaceuticals are potentially much more straightforward to both design and develop compared to small-molecule drugs or to large macro-molecular biopharmaceuticals. This is important given the ever-increasing cost of drug discovery and development.

What is your role at the university?

I have two roles at Queen Mary University of London. The first is as Vice Principal Research and Innovation, working to create an environment that stimulates research and brings teams together around big research challenges. The second is as a Professor of Chemical Engineering, where I lead a team of engineers and scientists creating new ways to carry out molecular separations, and use these separations to drive innovation in organic processes.

Briefly describe what work you have done in oligonucleotides and what your team is involved in.

My team is heavily focused on synthesising oligos in the liquid phase. We use iterative or convergent synthesis, coupled to membrane separation, which is an alternative to the current paradigm of solid phase synthesis. This means we can monitor the reactions to check they are complete, leading to a high purity which reduces costs of production. We can easily work with alternative chemistry types, and because our reactions are liquid phase we can easily adapt to new or different oligo chemistries. We call our new platform Nanostar Sieving.

What are some of your recent exciting findings?

We are working to increase the purity of the oligos we make to over 95% without chromatography. We recently passed 90% purity making a 20 mer anti-sense oligo with 2'methoxy chemistry. We have also shown that we can carry out fast and clean oxidation to yield combinations of phosphodiester and phosphorothioates on the backbone. We recently founded EXACTMER, a start-up that is working to commercialise Nanostar Sieving, and we are working with some of the leading pharma companies in the oligo space towards large scale, more economic manufacture.

Why is it so important to investigate the synthesis of oligonucleotides?

Lowering the price of these treatments through reduced oligo production costs will make them more accessible and affordable for healthcare systems, allowing new treatments for previously unresponsive medical conditions. Further, if production costs can be lowered, oligonucleotide therapies can be used to address diseases with large patient populations, such as diabetes and cardiovascular disease, in more effective ways. Specifically, oligos are usually delivered through a limited number of injections per year, in contrast to daily doses of drugs as pills and tablets. Research suggests that nearly half of people prescribed pills are on the wrong dose or fail to take the drugs properly to schedule, and so a limited number of annual injections from a medical professional can be a major improvement.

What do you think the future holds for oligonucleotides?

Growth – more candidates, wider range of diseases and a reduction in manufacturing cost leading to more widespread use.

Andrew will be speaking at the event on Day 2: Nanostar Sieving For Liquid Phase Synthesis Of Oligonucleotides.