What do you think are likely to be the most exciting developments for the cell and gene therapy industry over the next couple of years?

Gene therapy has been developing candidate products for the treatment of genetic and acquired diseases for almost 25 years, but there are practically no products yet on the market. Only one gene therapy product received marketing authorization in Europe - Glybera - although it isn’t sold yet due to pricing issues. In the last few years, however, clinical trials have shown the remarkable efficacy and safety of gene therapy for many diverse indications, such as blindness, hemophilia, immunodeficiencies, inherited anemias and importantly immunotherapy of cancer with CAR-T cells. The challenge for the industry is now to transform these clinical successes into marketed products. I believe we are going to see a few examples of this in the next couple of years. The successes of gene therapy and the favourable market situation have attracted very substantial investment into the creation of an impressive number of spin-offs and start-up biotechnology companies. Even the large pharmaceutical industry, after a decade of complete lack of interest, is now joining the community, and licensing more and more promising new therapies. This is unprecedented in the field; it’s a very exciting time.

What do you think are the biggest challenges the cell and gene therapy industry is facing at present?

The major challenge is the complexity of cell and gene therapies, which makes development of commercial products technically and logistically difficult. An example is the use of CAR-T cells for immunotherapy of cancer: this is an ex vivo therapy, which requires genetic modification of T cells with viral vectors, and a patient-specific therapy, which requires the development of a different product for each different patient. The same is true for genetically corrected hematopoietic stem cells, at the basis of some spectacular clinical successes in gene therapy for immunodeficiencies or lysosomal storage disorders. These products are based on relatively long and complex manufacturing processes and require complex logistics, with cells coming from patients and going back to patients after manufacturing. It is not obvious how to build an industry and market products around such complex logistics. The current legislation requires that both viral vectors and patient-specific cells are manufactured in pharmaceutical establishments and quality controlled as if they were conventional drugs or biological products, like vaccines or monoclonal antibodies. These, however, are patient-specific products, which could be manufactured in hospitals with less complexity and at a lower cost should the technology and legislation allow this to happen. Today, the big challenge for the industry is developing technology that will eventually allow bed-side production of genetically modified cells with the same quality and safety standards as in a centralized manufacturing facility.
Another example of the challenges the industry is facing is mass production of viral vectors for direct injection in patients, an entirely different class of products. Most in vivo gene therapies are based on such vectors, AAV for example, that are required at high or very high doses and for which the manufacturing technology is still primitive, complex and expensive. The reason for this is historical: the industry entered this field only recently, while the academia, which has carried the burden of developing gene therapy for over two decades in a climate of scepticism and with limited resources, has never made any significant effort to develop robust, scalable and economic production technology.

Not surprisingly, though, this is not the job of academic scientists and clinicians. Today, a typical GMP lot of an AAV vector destined to systemic administration is sufficient to treat a couple of dozes of patients at best, and it’s very expensive. Nobody knows yet how to manufacture AAV vectors at a scale that would be suitable to treat hundreds or thousands of patients worldwide. This practically limits this class of products to rare diseases. We definitely need a technology breakthrough here.

Viral vectors vs. non-viral vector systems are a hot topic of debate for the pharmaceutical industry at present. What do you think are the biggest challenges associated with this area currently and how do you think these challenges should be overcome in the future?

For gene delivery, almost everything that has been tested in clinical trials so far is based on viral vectors. Non-viral systems are far from having the efficiency of a virus-derived product, they are easier to manufacture but their application is still very limited. The exceptions are the recent development of small DNA- or RNA-based products, designed to interfere with normal gene regulation rather than providing entire genes to the cells. Examples of these are antisense oligonucleotides interfering with RNA splicing, or small catalytic RNAs, both currently under development for the treatment of neuromuscular diseases. For this class of products, manufacturing is not an issue. The challenges come instead from their short life in vivo, which requires frequent re-administration through routes that are sometimes difficult and always in hospitals or specialized structures. Frequent re-administration is often associated with toxicity or immune reaction, which limit efficacy to the short term: a problem for diseases affecting patients for their life time. A recent development, which may revolutionize gene therapy in the near future, is gene editing, or the direct correction of the human genome. This is still an experimental technology, which already showed its formidable power and potential in many non-medical fields. Gene editing is essentially based on non-viral technology, and although at the moment it’s still in a very early pre-clinical stage, we may see some clinical trials using this technology in the next few years. It’s a little too early to say, but this could be the very field where non-viral technology may become dominant. In terms of commercial development, though, I would say the products that we will see on the market in the next 3-5 years will be entirely based on viral vectors or a combination of viral vectors and cells. I previously made the example of CAR-T cells but it’s these days’ news that the European Medicines Agency issued a favourable opinion to GSK for the marketing authorization of Strimvelis, a genetically modified stem cell-based product for the treatment of a very rare immune disorder, ADA deficiency. This will be the first combined cell and gene therapy product to reach the market, great news for the field. I think we will see more of this kind of products on the market soon.
You will be presenting gene therapy for inherited blood diseases, from viral vectors to gene editing at this year’s congress. Why is this a particularly hot topic of discussion at present and what will drive these developments?

What we are discussing is the use of genetically modified stem cells as a technology platform for classical as well as gene editing-based gene therapies. Despite the complex logistics I mentioned before, stem cells are a very powerful tool, which can potentially be used to treat hundreds of diseases, and not only blood diseases. The platform is conceptually simple, we insert therapeutic genes into stem cells by using a viral vector, and then transplant them into patients using technology that is routine in all developed countries, bone marrow transplantation. Gene therapy adds genetic modification to a platform that is currently used to treat leukemias, lymphomas and other diseases, and expands enormously its potential to areas like metabolic or even infectious diseases. Stem cells are the most obvious target also for gene editing technology. In the near future, we hope to replace cumbersome viral vector technology with non-viral delivery tools that can then directly edit the gene to correct a mutation or provide cells with useful new functions. Interestingly, the first application of gene edited cells is a knock-out of a gene that HIV requires for infecting human T-cells, the CCR5 co-receptor. The booming CRISPR-Cas technology will certainly have an impact on genetic modification of stem cells very soon. The technology is still young, though, and I predict it will take a little more time than most people think to reach prime time. We should try not to repeat the mistakes of the past in the gene therapy field: too much hype creates expectations that cannot be met, and eventually backfires.

Career & Experience:

**Fulvio Mavilio**, Ph.D., is Scientific Director of Genethon (Evry, France), and Professor of Molecular Biology and University of Modena and Reggio Emilia (Modena, Italy). He was Director of Discovery of Molmed S.p.A. (2002-2005) and founder and Chief Scientific Officer of Genera S.p.A. (1999-2002). He had previously served as co-Director of the San Raffaele Gene Therapy Program in Milan (1995 to 2002), as director of the Molecular Hematology unit of the San Raffaele Institute (1989 to 1995), and as scientists at the Istituto Superiore di Sanità in Rome (1980 to 1986), Italy. Prof. Mavilio graduated in Biology in 1976 and obtained a Ph.D. in Medical Genetics in 1979 at the University of Rome, and trained as an NIH Fellow at the Wistar Institute in Philadelphia, PA, from 1986 to 1988. He is an expert and a pioneer in the fields of gene therapy and stem cell research, and author of over 180 articles in major international journals. He is a member of EMBO and of the Board of the American Society of Gene and Cell Therapy.

**Fulvio Mavilio** will be speaking on Day 2 of our 2nd Annual Cell and Gene Therapy Congress in the Cell Therapy Bioprocessing and Manufacturing stream: Gene Therapy for Inherited Blood Diseases, from Viral Vectors to Gene Editing.