Your work in the RNA Biology and Biotechnology laboratory covers a variety of areas, could you describe your primary interests and what you are hoping to achieve through your research?

At present my lab has two main research interests. Firstly, we study some very small RNA molecules called microRNAs (miRNAs) that have only recently been discovered. Due to their size, these RNA molecules were overlooked for a long time, but it has become clear in the last decade that thousands of them are encoded in the genomes of all organisms, and play a crucial role in cells, fine-tuning the production of functional proteins. We are developing a cure for a neurodegenerative disease, some retinal dystrophies and some metabolic diseases.

What is the significance of RNA, and how does it differ from DNA?

The difference between DNA and RNA is all in their names; ribonucleic acid (RNA) has a hydroxyl group attached in a specific position to each of the sugars (riboses) that compose it, while deoxyribonucleic acid (DNA) does not. This seemingly minor difference makes RNA much more flexible than DNA, resulting in a molecule that can adopt many different structures and acquire an array of functions. At the same time, RNA can in some cases use these hydroxyl groups to attack and cut chemical bonds, thus functioning as an RNA enzyme or ribozyme. Finally, as with DNA, RNA can bind with other RNA molecules through base-pairing, which dictate that only complementary sequences will bind with each other, making RNA binding very specific. These properties – flexibility, catalytic activity and specificity – make RNA a fantastic tool for inactivating specific genes, either to discover their functions or for therapeutic intervention.

Could you briefly give an overview of the different roles of the various RNA subtypes?

In the last 50 years, scientists have substantially confirmed Francis Crick’s ‘Central Dogma of Biology’ – DNA makes RNA makes protein – but have also found more and more examples of RNAs which do not make proteins. These non-coding RNAs come in many different varieties. Ribosomal RNAs (rRNAs) and transfer RNAs (tRNAs) collaborate in the construction of proteins; small nuclear RNAs (snRNAs) have an important role in RNA splicing; and small nucleolar RNAs (snoRNAs) intervene in the chemical modification of other RNAs. Two recent additions to the family are miRNAs and short interfering RNAs (siRNAs), the latter of which take part in a process called RNA interference that protects the cell from invading RNA molecules such as viruses.

Do you think that science is on the cusp of introducing gene therapies for inherited disease?

I firmly believe that gene therapy will soon allow us to cure most genetic diseases. The recent successes in clinical trials with acute lymphocytic leukaemias, Leber’s congenital amaurosis, adrenoleukodystrophy, multiple myeloma and Parkinson’s disease, among others, support this view. About a year ago, the first ever gene therapy treatment, Glybera, was approved for clinical use in Europe and the US as a cure for lipoprotein lipase deficiency. This came about as a result of more than 25 years of clinical trials; optimisation of safer and more efficient delivery vectors; and technological improvements.
IT IS NOW widely acknowledged that RNA plays an important role in almost every aspect of gene expression, and that most human genetic diseases result from abnormalities in its metabolism. Following decades of research, RNA is now understood not only to carry genetic information, but to act as both a catalyst and an influence on the sequence-specific recognition and processing of other RNA molecules. Subsequently, the growing body of knowledge concerning RNAs is opening up exciting and unprecedented avenues for research, both in terms of understanding the genetic causes of diseases and identifying targets for novel therapeutics.

At the forefront of this burgeoning research into RNA are a series of studies being undertaken in the Centre for Integrative Biology at the University of Trento, Italy, which are seeking to shed light on the possibility of using microRNAs (miRNAs) as therapeutic targets and highlight the role of RNA-induced exon-skipping in gene therapy. Led by Dr Michela Alessandra Denti, and making full use of the world-class facilities within the University’s Laboratory of RNA Biology and Biotechnology, the research is expected to make great strides in advancing the use of RNA-based techniques for both gene therapy and applied research. The group hopes that this work could lead to significant improvements in the diagnosis and treatment of a variety of debilitating and potentially fatal genetic diseases, improving the lives of people around the world.

THE BASICS OF RNA
A large part of RNAs influence over the human genome lies in its ability to switch off specific genes, the exact mechanisms behind which are not fully understood. Denti’s involvement in RNA research stretches back to the 1990s when, as an undergraduate at the University of Pisa and later a PhD student at the Scuola Normale Superiore she became interested in elucidating the function of a naturally occurring ribozyme. By examining this ribozyme – a catalytic RNA understood to have significant potential for use in therapeutics, due to its ability to cut harmful messenger RNAs (mRNAs) – she hoped to inactivate gene functions in vivo. “In particular, we were hoping to obtain high target specificity, we wanted to switch off only the gene of interest and none of the others, minimising the risk of side-effects,” Denti recalls.

Molecular treatments for major diseases
Ongoing research at The University of Trento, Italy, is opening up the possibility of developing better diagnostic tools and therapeutics for a range of aggressive genetic diseases and cancers.
During the 1980s and 90s, molecular biologists were enormously hopeful about the potential of ribozymes for therapeutically switching off specific genes, and in 1989 Drs Sidney Altman and Thomas R Cech won the Nobel Prize in Chemistry for their work describing the catalytic properties of RNA. While much of this early optimism has since proved misplaced, the research undertaken during this period revealed that RNA is not simply a messenger for carrying information from genes to proteins, and neither is it solely involved in dictating the structure of ribosomes. In fact, RNA is able to both store genetic information and to operate as an enzyme. Subsequently, there emerged much evidence to support the hypothesis that self-replicating RNA molecules were the precursor to current life on Earth, a notion which is now widely accepted.

EXON-SKIPPING

Alongside this work, the group is carrying out studies into therapeutic modulation of RNA splicing to develop cures for Frontotemporal Dementia with Parkinsonism linked to chromosome 17, and for some types of retinal dystrophies. By introducing small RNA molecules, we mask the mRNA to the attack of the splicing machinery, inducing it to jump certain portions of the mRNA - a process we call ‘exon-skipping’.

INTERORGANISATIONAL COLLABORATION

The groundbreaking work being carried out by Denti and her colleagues is only possible via productive partnerships and networks at local, national and international levels. These have crucially included collaborations with researchers from a huge variety of disciplines, giving the project a holistic approach which is important to appreciate the complexity of these processes. While the Trento group contributes its extensive knowledge of RNA, Denti is keen to highlight how the other groups bring their specific, complementary expertise to the process. “Only through collaboration has our cutting-edge research been made possible, and only in this way will it continue into the future,” she explains.