The research of the laboratory has two main themes: the study of the role of non-coding RNA induced by DNA damage in the neurodegeneration of Amyotrophic Lateral Sclerosis, and the characterization of the role of DICER in the prevention of breast cancer.

The of non-coding RNA induced by DNA damage in ALS role

Il The genetic material present in our cells suffers thousands of threats every day resulting in DNA damages that need to be promptly repaired to prevent the cells from a premature death. Our cells developed a coordinated signalling procedure called the DNA damage response (or DDR) that senses the DNA damage and quickly repair the damage. Unfortunately, it has been shown that motor-neurons of patients affected by ALS may fail to efficiently repair these damages which progressively accumulate in the cell thus leading to neurodegeneration. However, the molecular mechanisms behind DNA damage accumulation in ALS motor-neurons still needs to be elucidated.
We and others research group, recently discovered a new class of small RNAs, named DDRNAs, needed for DDR activation and DNA damage repair. To produce DDRNAs, cells utilise two proteins, DROSHA and DICER that, when inactive hamper the ability of the cell to recognize and repair the damage. Importantly, some mutations that predispose to ALS occur in genes encoding for TDP43 and FUS two RNA-binding proteins that stimulate the functions of DROSHA and DICER.
We observed that TDP43 help the cells to sense DNA damage, likely by controlling the synthesis of DDRNAs and hypothesized that TDP43 mutation could be responsible for the accumulation of DNA damage in cells of ALS patients. In addition we discovered that the use of enoxacin, a compound with proved beneficial effects on neuromuscular function of ALS mouse models, increases DDRNA biogenesis and induces faster DNA repair.
Starting from these findings we aim to demonstrate that ALS-associated neurodegeneration is caused by defects in DDR signalling and DNA repair due to an inefficient production of DDRNAs. By uncovering a novel molecular mechanism behind DNA damage accumulation in ALS, this project will help to provide a new therapeutic approach for the treatment of the disease.

A novel Role for DICER in Breast Cancer prevention

The project aims to characterize a new molecular mechanism relevant to the prevention of the onset of breast cancer associated with a defect in DNA repair mechanisms by homologous recombination with consequent accumulation of DNA damage and genomic instability.
Recently we have characterized the existence of a new class of non-coding RNA, processed by the enzyme DICER that are required for the activation of the DNA damage response, the DDRNA.
Altri gruppi hanno dimostrato che i DDRNA prendono parte nella ricombinazione omologa durante la riparazione. Other groups have shown that DDRNA take part in homologous recombination during repair. Since it is known that the expression of DICER is frequently reduced in breast cancer cells, especially in the more advanced and aggressive stages, we intend to investigate whether DICER and its RNA products required for shelter by homologous recombination play a role of oncosuppressors in these tumors. For the same principle we intend to test the sensitivity of cell lines from tumors with reduced expression of DICER, the inhibitor of PARP, known for its effectiveness in deficient cells for homologous recombination. The project has as objectives both the characterization of a new mechanism at the base of genomic instability associated with breast cancer and that of testing if triple breast cancer negative cell lines that show DICER repression but the wild-type expression for BRCA1 / 2 proteins are more sensitive to PARP inhibition by the use of Olaparib (Lynparza) than cells with normal DICER expression levels. We also plan to test whether the use of drugs that stimulate the existing DICER activity on the market (ex: Enoxacin) can recover the efficiency of homologous recombination of mutated BRCA1 / 2 cell lines. Finally we are investigating whether the secretory cytokine phenotype (SASP) of senescent cells within human breast tumor samples, known to stimulate tumor progression, inversely correlates with DICER expression levels.