# RIA Research and Innovation action

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## Introduction

Recent evidences suggest that metabolites themselves can be oncogenic by altering cells. The advances in cancer metabolism research, over the last decade, have enhanced our understanding regarding the aerobic glycolysis and other metabolic alterations that are associated with cell growth and proliferation.
The objective of this work is to demonstrate that, under condition of changes of cellular microenvironment, the product of gene P-53, the protein p-53 lost its role of stopping division cells and become aggressive in the carcinogenesis process.
Research within the Cancer Genetics Program is wide ranging. It includes identifying and studying genes associated with childhood cancer risk; analyzing molecular and cell biology pathways associated with development and progression of cancers; identifying molecules that might represent viable targets for novel drug therapies
Most important cell-regulatory mechanisms of energetic metabolic pathways, in mammalian T cells and B cells are: death receptors, caspases, mitochondria, the Bcl-2 family proto-oncogene, tumor suppressor gene TP53, TNF, and nuclear translocation factor, NF-Kb and recently Micro RNAs (miRNAs) which are small non-coding RNAs that act at the posttranscriptional level to regulate protein expression.
The p53 gene is responsive to a large number of environmental stressors and regulates maintenance of genomic stability, changes in oxidative stress and mtDNA copy number, and adjacent regions to p53 encode for proteins with important roles cellular function.
"In the presence of some type of environmental stressor, the tumor suppressor p53 stops cell division to allow the repair of damaged DNA.
A dysfunctional apoptotic pathway may lead to the development of cancers. Due to the sensitivity of the intrinsic pathway, tumors arise more often through the intrinsic pathway than the extrinsic pathway . A very common cause of malignant tumors through the intrinsic pathway is a mutation in the p53 protein (tumor-suppressor protein). Besides regulating apoptosis, p53 also regulates the checkpoints of the cell cycle, DNA repair, senescence, and genomic integrity.
A mutation causes the p53 gene to lose any of its functions will inevitably lead to carcinogenesis by letting the cell grow indefinitely, without any regulation. The p53 gene has been mapped in chromosome 17. In the cell, p53 protein binds DNA, stimulating another gene to produce the protein p21 that interact with cycle cell in division, stimulating a protein of stop division (cdk2). Another important factor in carcinogenetic process is the balance between the pro-apoptotic and anti-apoptotic members of the Bcl-2 family. In a tumor cell, a mutation in the Bcl-2 gene results in increased expression will suppress the normal function of the pro-apoptotic proteins BAX and BAK, leading to malignancy.

In the normal cell, the p53 protein binds DNA, stimulating another gene to produce a protein called p21, which interacts with a cell division stimulating protein (cdk2) [11]. When p21 forms a complex with cdk2, the cell cannot pass through to the next stage of cell division, and remains arrested in G1.
The p53 protein product of a TP53 mutant gene cannot bind DNA in an effective way, and as a consequence, the p21 protein is not made available to act as the stop signal for the cell cycle/cell division. Therefore, cells divide uncontrollably and form tumors [4] Not surprisingly, there is an increased frequency in the amplification of

the ubiquitin ligases protein (MDM2) involved in the mechanism for the down regulation of p53 activity through ubiquitin-dependent proteosomal degradation of p53.
The anabolic metabolism in B and T cells from malignant diseases there is under a complex regulatory control directed of membrane receptors, associated with growth factors signals of transduction in transformed cells.
P53 has been shown to promote hematopietic stem cells (HSCs) quiescence and self-renewal with recent studies showing that deficiency of p53 likely promotes acute myeloid leukemia (AML) by eliminating its ability to limit aberrant self-renewal in hematopoietic progenitors. Micro RNAs (miRNAs) are small non-protein-coding RNAs that regulate gene expression by inhibiting the translation or catalyzing the degradation of target mRNAs. Since the first miRNA, lin-4, was identified in 1993, miRNAs have been shown to play critical roles in the regulation of many biological processes including cell differentiation, proliferation, and apoptosis, with significant influences on normal and malignant hematopoiesis.
In this context the nuclear p-53 proteine was showed that protect the cell of a malignant process, and only citoplasmatic p-53 proteine, by its izoforms, in modified citoplsmatic medium, by high concentration of anaerobic ATP, drives at cancer.
This energetic level could initiate the process of carcinogenesis, by the supression of anti-oncogene proteins, from its normal activity. Management of bionergy cells, from cancer cells, on glicolitic pathway, can stop the processs of carcinogenesis.
- Energy levels of the metabolic pathways in malignant B and T lymphocytes in Review" ,the chapter presents the latest evidence from the literature on cellular metabolites that may be oncogenic by modifying cell signaling and blocking cellular differentiation. Advances in cancer metabolism research in the last decade have increased our understanding on aerobic glycolysis, anaerobic and other metabolic ch"anges that are associated with cell growth and proliferation.
Blocking apoptosis in malignant diseases may be due to the high concentration of ATP from anaerobic metabolism. Energy difference between anaerobic ATP B and T lymphocytes in peripheral blood samples from hematopoietic malignancies measured by bioluminescence was 2.68 µM ATP, a value that appears as an energy transfer between normal B cells and T cells. The energy level can initiate the process of carcinogenesis by suppressing the activity of anti-oncogene proteins.
It is concluded that anabolic metabolism in B and T cells in hematological malignancies are under complex regulatory control, directed by receptors on the cell membrane associated with an increase in signal transduction in cells transformed into malignancy.

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See all projects funded under this programme / topic

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## EXCELLENT SCIENCE - Future and Emerging Technologies (FET)

### Specific objective

The specific objective is to foster radically new technologies with the potential to open new fields for scientific knowledge and technologies and contribute to the European next generation industries, by exploring novel and high-risk ideas building on scientific foundations. By providing flexible support to goal-oriented and interdisciplinary collaborative research on various scales and by adopting innovative research practices, the aim is to identify and seize opportunities of long-term benefit for citizens, the economy and society. FET will bring Union added value to the frontiers of modern research.
FET shall promote research and technology beyond what is known, accepted or widely adopted and shall foster novel and visionary thinking to open promising paths towards powerful new technologies, some of which could develop into leading technological and intellectual paradigms for the decades ahead. FET shall foster efforts to pursue small-scale research opportunities across all areas, including emerging themes and grand scientific and technological challenges that require close collaboration between programmes across Europe and beyond. This approach shall be driven by excellence and extends to exploring pre-competitive ideas for shaping the future of technology, enabling society and industry to benefit from multi-disciplinary research collaboration that needs to be engaged at European level by making the link between research driven by science and research driven by societal goals and challenges or by industrial competitiveness.

### Rationale and Union added value

Radical breakthroughs with a transformative impact increasingly rely on intense collaboration across disciplines in science and technology (for instance, information and communication, biology, bioengineering and robotics, chemistry, physics, mathematics, medicine modelling, Earth system sciences, material sciences, neuro- and cognitive sciences, social sciences or economics) and with the arts, behavioural sciences and humanities. This may require not only excellence in science and technology but also new attitudes and novel interactions between a broad range of players in research.
While some ideas can be developed on a small scale, others may be so challenging that they require a large collaborative effort over a substantial period of time. Major economies worldwide have recognised this, and there is growing global competition to identify and pursue emerging technological opportunities at the frontier of science which can generate a considerable impact on innovation and benefits for society. To be effective, these types of activities

may need to be built up quickly to a large scale by a common European effort around common goals to build critical mass, foster synergies and obtain optimal leveraging effects.
FET shall address the entire spectrum of science-driven innovation: from bottom-up, small-scale early explorations of embryonic and fragile ideas to building new research and innovation communities around transformative emerging research areas and large collaborative research initiatives built around a research agenda aiming to achieve ambitious and visionary goals. These three levels of engagement each have their own specific value, while being complementary and synergistic. For example, small-scale explorations can reveal needs for developing new themes that can lead to large-scale action based on appropriate roadmaps. They may involve a wide range of research players, including young researchers and research-intensive SMEs, and stakeholder communities (civil society, policymakers, industry and public researchers), clustered around evolving research agendas as they take shape, mature and diversify.

### Broad lines of activities

While FET aims to be visionary, transformative and unconventional, its activities shall follow different logics, from completely open to varying degrees of structuring of topics, communities and funding.
The activities shall give firmer shape to different logics for action, on the appropriate scale, identifying and seizing opportunities of long-term benefit for citizens, the economy and society:

### (a) FET Open

By fostering novel ideas ('FET Open'), FET shall support early stage science and technology research exploring new foundations for radically new future technologies by challenging current paradigms and venturing into unknown areas. A bottom-up selection process widely open to any research ideas shall build up a diverse portfolio of targeted projects. Early detection of promising new areas, developments and trends, along with attracting new and high-potential research and innovation players, will be key factors.

### (b) FET Proactive

By nurturing emerging themes and communities ('FET Proactive'), FET shall, in close association with the societal challenges and industrial leadership themes, address a number of promising exploratory research themes with the potential to generate a critical mass of inter-related projects that, together, make up a broad and multi-faceted exploration of the themes and build a European pool of knowledge.

### (c) FET Flagships

By pursuing grand interdisciplinary scientific and technological challenges ('FET Flagships'), FET shall, taking into full account the outcome of FET preparatory projects, support ambitious large-scale, science and technology-driven research aiming to achieve a scientific and technological breakthrough in areas identified as relevant in an open and transparent manner involving the Member States and relevant stakeholders. Such activities could benefit from the coordination between European, national and regional agendas. The scientific advance should provide a strong and broad basis for future technological innovation and economic application, plus novel benefits for society. These activities shall be realised using the existing funding instruments.
40 % of FET resources will be devoted to FET Open.

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