# EXPERIMENTAL THERAPEUTICS PROGRAMME

**JOAQUÍN PASTOR** Programme Director

"Interrogate biology with chemistry and you will get responses that can trigger unimaginable research and discoveries."

The Experimental Therapeutics Programme (ETP) serves as a bridge between basic research results in cancer biology (i.e. novel therapeutic targets and hypothesis) and the development of potential antitumour drugs. This is achieved by the application of early drug discovery phases to obtain advanced compounds with proven *in vivo* Proof of Concept (PoC) results. ETP assists target validation activities by providing high quality chemical probes and participates in the identification of novel targets using its expertise in target deconvolution.

*CDK8 inhibitors.* As previously reported, we selected our first leads, ETP-27 and ETP-93, as dual CDK8/Haspin inhibitors, which have yielded positive results in PoC studies after oral (PO) administration. Now, we have added ETP-18, a highly selective orally bioavailable CDK8 inhibitor, to our set of advanced leads. ETP-18 has demonstrated good biomarker modulation (pSTAT1) after PO administration in pharmacokinetics and pharmacodynamics (PK/PD) studies in MOLM13 xenografts. Currently, we are performing *in vivo* efficacy experiments to complete our PoC studies. Importantly, we have started toxicity studies of our advanced leads in rats to establish their therapeutic index. The results of these experiments will determine the destiny of these series of CDK8 inhibitors regarding their further development.

*Haspin and Mastl Inhibitors (in collaboration with Marcos Malumbres' laboratory).* We have generated 2 distinct chemical series of highly potent Haspin inhibitors, which have proven to be very specific after profiling against more than 450 kinases. These molecules have been profiled against a diverse panel of 40 cell lines. Haspin inhibitors showed limited antiproliferative potential as single agents. Now, we are evaluating their effect in combination with clinical antitumour agents; the results of this study will help to define the therapeutic scope for these inhibitors. During 2018, we completed the Structure-Activity-Relationships (SAR) of 2 families of potent Mastl inhibitors; this information has helped to deploy a hit generation campaign to increase the chemical diversity of our Mastl inhibitors. The generation of diverse Mastl inhibitors will increase our chances to identify the most interesting series in terms of potency, cell activity and above all off-target selectivity for pharmacological target validation studies. Interestingly, we have identified the solvent accessible areas in our initial Mastl inhibitors; this information has been used in the design of Mastl-Protacs to target the degradation of this kinase.

*TRF1 (in collaboration with Maria Blasco's laboratory). TRF1 modulators as potential cancer therapeutics.* As reported earlier, we discovered a series of TRF1 inhibitors (ETP-946 series 2) with unknown molecular mechanism of action. Therefore, several target deconvolution strategies were put in place to identify its target. During 2018, we focused our efforts on the preparation of reversible and irreversible affinity probes with proven TRF1 inhibition capacity. As an example, ETP-093, an irreversible probe, has been used in a first pull-down experiment rendering several nuclear proteins as potential target candidates. We are doing replicates of this study in order to have a final selection of candidates for further validation. Furthermore, we have progressed in the SAR generation of series 2 by the synthesis of numerous analogues. These compounds have been included in a recently filed patent application. We have gathered information about the drug-likeness of this series and we are now targeting its optimisation as well as the reinforcement of its intellectual property (IP). These activities are part of an awarded *CaixaImpulse* project (M. Blasco's lab) in which ETP participates. Importantly, we have contributed to the discovery of *novel cellular pathways able to modulate TRF1 binding to telomeres.* As reported earlier, ETP has helped to establish the connection of the PI3K/AKT axis and TRF1. During 2018, we identified other cell signalling pathways involved in TRF1 regulation (currently under detailed investigation at M. Blasco's lab) by the screening of our ETP-antitumour library.

Finally, we have also helped other CNIO groups to carry out screening campaigns, both targeted and phenotypic, and have supported the follow up of the identified hits in several projects.

# MEDICINAL CHEMISTRY SECTION

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## OVERVIEW

The Medicinal Chemistry Section is part of the interdisciplinary Experimental Therapeutics Programme that is dedicated to early Drug Discovery in the oncology field. Our aim is to discover new anticancer agents based on the hypotheses and targets generated by CNIO's Basic Research Groups; this is done in close collaboration with these Groups. Medicinal Chemistry activities start with the identification of hits through High Throughput Screening (HTS) campaigns from targeted or phenotypic assay or hits generated in our Section by applying Rational Drug Design Strategies; these are then optimised to obtain novel lead compounds with *in vivo* activity in different animal models. For hits obtained from phenotypic screenings, we help to decipher the mechanism of action responsible for the observed phenotype, synthesising affinity probes that will be used for cellular localisation (imaging techniques) and extracting the target/s (pull down experiments). We are also developing PROTACs (proteolysis targeting chimeras) as promoters of cell protein degradation to establish their applicability across diverse drug discovery projects.

**"We have successfully designed and synthesised an irreversible affinity chemical probe of ETP-946 that is to be used for imaging and pull-down/proteomics analysis experiments; the aim is to decipher the mechanism of action of this TRF1 modulator."**

## RESEARCH HIGHLIGHTS

### Cyclin-dependent protein kinase 8 inhibitors (CDK8i) project

ETP-93, with demonstrated proof of concept studies (PoC) in mouse models, and ETP-18 were identified as potent, selective and orally bioavailable CDK8 inhibitors. We are involved in the multigram scale up of these compounds in order to perform toxicity studies in rats, as well as to determine if the compounds/inhibition of the target is safe enough to progress them to the next phases of drug development. With these results in hand, we will be able to initiate the transfer of our results to companies interested in developing our compounds into drugs. Additionally, we will also perform PoC studies (efficacy and biomarker modulation) with ETP-18.

### Microtubule-associated serine/threonine protein kinase-like (MASTL) inhibitors

In collaboration with the CNIO Cell Division and Cancer Group, we continue with the exploration around the chemical series identified to obtain potent and selective compounds. Strategies to generate MASTL-PROTACs are also contemplated in order to generate degrader compounds of the protein; the first PROTACs have been synthesised with moderate MASTL activity (FIGURE). We are initiating a hit generation phase to obtain novel Mastl inhibitor hits.

### HASPIN inhibitors

Highly selective hits identified from 2 previously generated chemical series were scaled up to be characterised *in vivo* in order to determine their pharmacokinetics in mice as well as to be used in the biological characterisation to study the relevance of HASPIN in cancer, including their effect in antiproliferative experiments as single agents and in combination with other antitumour agents. We continue with the chemical exploration around the hits to conclude the SAR activities and to define the scope of their kinase activity.

### Telomeric repeat binding factor 1 (TRF1) inhibitors

This project is undertaken in collaboration with the CNIO Telomeres and Telomerase Group (TTG). ETP-946 was identified as a TRF1 modulator under screening assay conditions, and we are currently working on deciphering its mechanism of action. One of the approaches that we have taken is to use affinity chemical probes. We generated SAR information from the chemical exploration in the hit-to-lead phase (approximately 150 compounds were synthesised), and with this information we identified those parts of the hit molecule at which to install linkers and synthesise probes. During this year, we accomplished synthesis of an irreversible affinity chemical probe (ETP-093), which contains photoreactive and reporter groups, made as small as possible to minimise the interference upon binding to the target proteins. The aliphatic diazirine photoreactive group of ETP-093 enables, after incubation with cells, short irradiation to generate the highly reactive carbene species that will react with the binding protein/s. The terminal alkyne reporter of ETP-093 was then used for subsequent target identification by conjugation to suitable reporters (biotin-$N_3$) using biorthogonal click chemistry conditions, which enable pull-down experiments. So far, we have performed the first pull down experiment and the proteomic analysis, which will be further repeated 3 more times for a robust interpretation of the results. Pull down experiments with the reversible affinity probe ETP-455 were generated. This chemical probe lacks the photoreactive group, so its binding with affinity protein/s is not covalent and we may lose some relevant information during the washing steps phase. Nevertheless, once we have finalised all the experiments, we will compare results between reversible/irreversible affinity chemical probes. We have filed a patent application to cover the chemical series of ETP-946. This project was recently awarded a grant from the *CaixaImpulse* programme and we are currently working on the optimisation of the drug-like properties of ETP-946 together with the generation of novel chemical space for patent reinforcement.

### Collaborations with other CNIO groups

We continue our collaborations with other researchers from the Centre, for instance, with Alejo Efeyan (Metabolism and Cell Signalling Group) performing stability, reactivity studies of the hits and synthesis of tools to help decipher their mechanism of action; and with Paco Real (Epithelial Carcinogenesis Group) for the synthesis of reference compounds. ■

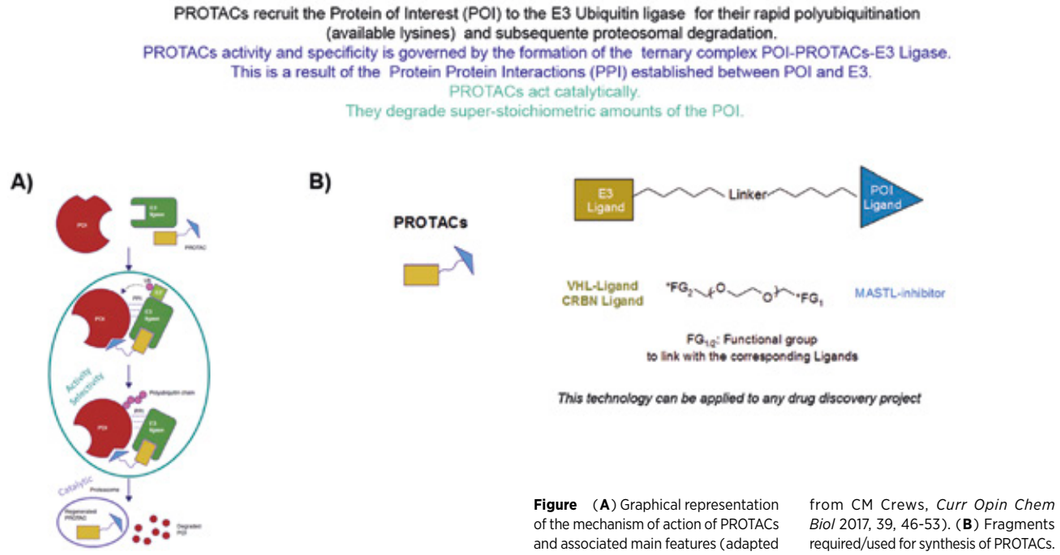


**Figure** (**A**) Graphical representation of the mechanism of action of PROTACs and associated main features (adapted from CM Crews, *Curr Opin Chem Biol* 2017, 39, 46-53). (**B**) Fragments required/used for synthesis of PROTACs.

**PATENT**


- Pastor JA, Blasco MA, Martinez S, Blanco-Aparicio C, García AB, Gómez-Casero E, Bejarano, L, Méndez-Pertuz M, Martínez P, García-Beccaria M (2018). Novel TRF1 modulators and analogues thereof. *EP18382659.3*.

# BIOLOGY SECTION

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## OVERVIEW

The early Drug Discovery (eDD) process encompasses screening campaigns for hit identification, hit generation and hit lo lead and lead optimisation phases, in order to end up with a lead compound able to demonstrate *in vivo* proof-of-concept. ADME – an acronym for absorption, distribution, metabolism and excretion – describes the disposition of a pharmaceutical compound within an organism. ADME properties influence the drug levels and the kinetics of drug exposure to the tissues, and hence influence the performance and pharmacological activity of the compound as a drug. It is fundamental to assess the parameters for ADME properties early on during the discovery stage, since they provide critical information that can help to better interpret the screening results and to design new molecules. Drug-like properties should be optimised in parallel to pharmacological activity against the target. For that reason, we perform ADME characterisation of the compounds during the initial steps of eDD projects and we carry out PK, PK/PD and distribution studies to validate the drug properties of our advanced molecules.

**"The screening of the ETP-antitumour library in the phenotypic TRF1 assay has enabled us to identify new signalling pathways modulating TRF1 levels that will contribute to a better understanding of TRF1 biology."**

## RESEARCH HIGHLIGHTS

During 2018, our Section was involved in several projects:

**Cyclin-dependent kinase 8 (CDK8)**

We started proof-of-concept studies in mouse models with ETP-18, a selective advanced orally bioavailable lead compound that demonstrated both plasma and tumour levels as well as biomarker modulation (pSTAT1), in a dose dependent manner up to 8 h after oral administration in PK/PD studies in MOLM13 xenografts. Tolerance and efficacy studies will be performed. In parallel, after pharmacokinetics studies of 3 more selective CDK8 inhibitors, we have identified ETP-24 as a backup of ETP-18.

To determine if the inhibition of the target by our compounds is safe enough to progress them to the next phases of drug development, we are running toxicity studies in rats with the leads ETP-93 (dual CDK8/HASPIN-i) and ETP-18 (selective CDK8-i), in comparison with known inhibitors.

**Microtubule-associated serine/threonine protein kinase-like (MASTL) and HASPIN**

These projects are undertaken in collaboration with the CNIO Cell Division and Cancer Group. For MASTL, we tested 85 new compounds in our biochemical assay with active human full length MASTL protein; 11% of them were tested as part of the hit generation phase and we have also tested our ETP-antitumour library to identify novel hits. One drug is under validation as a putative MASTL-inhibitor. For HASPIN, we tested in biochemical and cellular assays, 42 compounds to complete the SAR exploration of the chemical series. We have evaluated the antiproliferative activity of highly selective HASPIN-inhibitors (S(35) of 0.025 and 0.007) from 2 different chemical series in a panel of 40 cell lines covering the more relevant tumour types. Now, we are evaluating their effect in combination treatments. We have also characterised in ADME assays representative compounds for the 2 chemical series. We have performed a preliminary pharmacokinetic study with 1 selected compound with good ADME properties and we are running a distribution study to validate it as a good tool compound for i*n vivo* proof-of-concept.

**Telomeric repeat binding factor 1 (TRF1)**

This project is carried out in collaboration with the CNIO Telomeres and Telomerase Group. A phenotypic assay to measure the association of TRF1 to telomeres has been used to test 30 compounds, which include ETP-946 analogues and its corresponding irreversible chemical probes. We have identified an active irreversible chemical probe, ETP-093, and we are running pull-down experiments with it. Several nuclear targets have been identified as potential targets and we want to validate them with 2 more pull-down experiments. In the meantime, we have used ETP-455, a reversible chemical probe, to perform pull-down experiments in triplicate. After comparison of the 3 experiments, we have identified 2 putative targets that we are trying to validate by orthogonal assays. We will compare the pull-downs with both reversible and irreversible chemical probes in order to select the best candidates. On the other hand, we have performed distribution studies with ETP-946 and have observed that the compound is distributed in tissues. Furthermore, by using a chemical biology approach, we have validated 3 more signalling pathways that were identified in the screening of the ETP-antitumour library that modulates TRF1 levels at telomeres; Maria Blasco's laboratory is deciphering the molecular mechanism behind this. These results are part of a patent application PCT/EP2018/074832. Finally, we have started a virtual screening with the aim of identifying disruptors of TRF1 dimerization (FIGURE).

**Collaborations with other CNIO Groups**

ETP-Biology continued providing support to follow-up on the results obtained from the screenings performed by the Brain Metastasis Group and the Metabolism and Cell Signalling Group. Moreover, we have provided support by testing and analysing the ETP-antitumour library, either alone or in combination, in order to identify: i) novel treatments of NSCLC mouse cell lines mutant in KRas with and without C-RAF and CDK4, in collaboration with the Experimental Oncology Group; and ii) novel modulators of Midkine expression, in collaboration with the Melanoma Group. ■

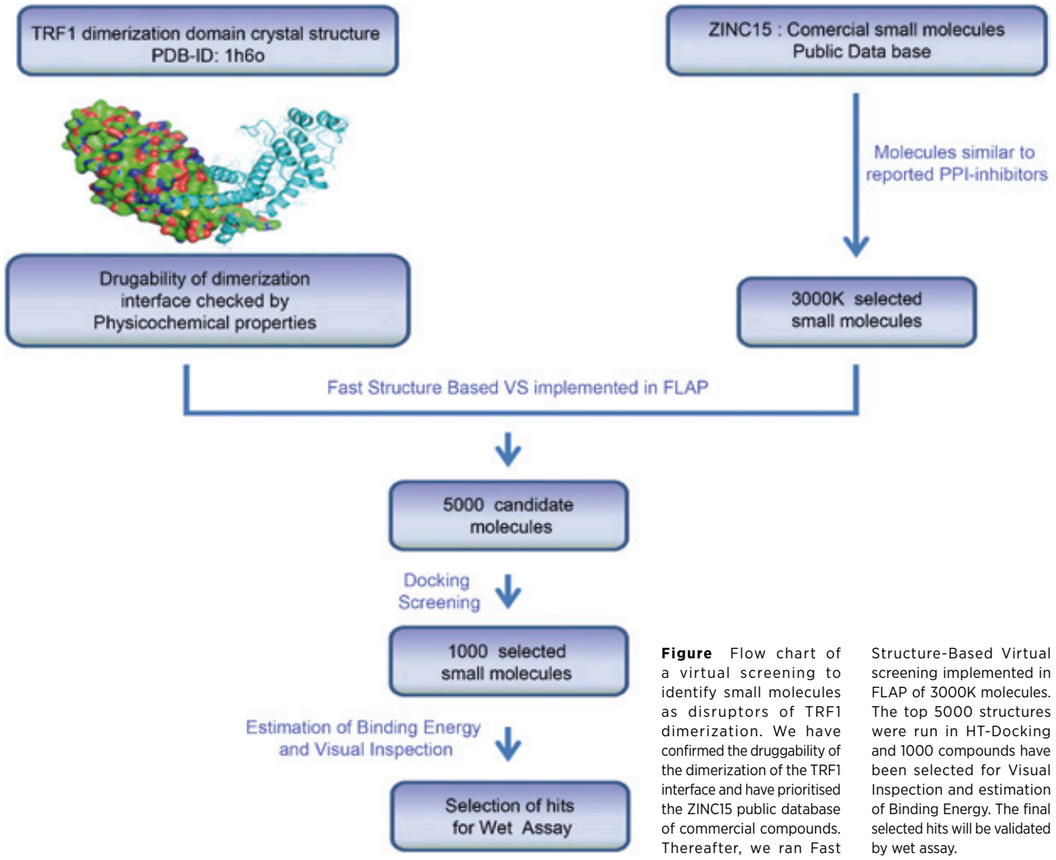


**Figure** Flow chart of a virtual screening to identify small molecules as disruptors of TRF1 dimerization. We have confirmed the druggability of the dimerization of the TRF1 interface and have prioritised the ZINC15 public database of commercial compounds. Thereafter, we ran Fast Structure-Based Virtual screening implemented in FLAP of 3000K molecules. The top 5000 structures were run in HT-Docking and 1000 compounds have been selected for Visual Inspection and estimation of Binding Energy. The final selected hits will be validated by wet assay.

**PUBLICATIONS**


- Priego N, Zhu L, Monteiro C, Mulders M, Wasilewski D, Bindeman W, Doglio L, Martínez L, Martínez-Saez E, Ramón Y Cajal S, Megías D, Hernández-Encinas E, Blanco-Aparicio C, Martínez L, Zarzuela E, Muñoz J, Fustero-Torre C, Piñeiro-Yáñez E, Hernández-Laín A, Bertero L, Poli V, Sanchez-Martinez M, Menendez JA, Soffietti R, Bosch-Barrera J, Valiente M (2018). STAT3 labels a subpopulation of reactive astrocytes required for brain metastasis. *Nat Med* 24, 1024-1035.
- Toledo RA, Garralda E, Mitsi M, Pons T, Monsech J, Vega E, Otero Á, Albarran MI, Baños N, Durán Y, Bonilla V, Sarno F, Camacho-Artacho M, Sanchez-Perez T, Perea S, Álvarez R, De Martino A, Lietha D, Blanco-Aparicio C, Cubillo A, Domínguez O, Martínez-Torrecuadrada JL, Hidalgo M (2018). Exome sequencing of plasma DNA portrays the mutation landscape of colorectal cancer and discovers mutated VEGFR2 receptors as modulators of antiangiogenic therapies. *Clin Cancer Res* 24, 3550-3559.


**PATENTS**


- Pastor JA, Blasco MA, Martinez S, Blanco-Aparicio C, García AB, Gómez-Casero E, Bejarano, L, Méndez-Pertuz M, Martínez P, García-Beccaria M (2018). Novel TRF1 modulators and analogues thereof. *EP18382659.3*.
- Blasco MA, Pastor JA, Bejarano L, Méndez-Pertuz M, Martínez P, Blanco-Aparicio C, Gómez-Casero E, García-Beccaria M (2018). Modulation of TRF1 for brain cancer treatment. *EP18382658.5*.

# CNIO - LILLY CELL SIGNALLING THERAPIES SECTION

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## SCOPE OF THE ELI LILLY - CNIO PARTNERSHIP

Eli Lilly and CNIO are collaborating on the identification and validation of novel targets in cancer immunometabolism. Our Section is funded through a research contract with Eli Lilly and focuses on the identification of small molecular weight molecules that regulate the metabolism of malignant cells, with the objective of killing them either directly, acting synergistically with other anti-tumour agents, or activating the anti-tumour immune response. Exploring how to better target these mechanisms would lead to better and more efficient therapeutic options.

A combination of *in vitro* and *in vivo* approaches is being utilised to obtain a complete understanding of tumour metabolic reprogramming. For this purpose, we have developed a series of biochemical and cell-based assays exploiting advanced techniques such as extracellular flux analysis (Seahorse technology), NMR, metabolomics and immunophenotyping. Finally, each target goes through an *in vivo* validation process using xenografts, allografts and mouse models developed at the CNIO that includes the use of non-invasive *in vivo* imaging technologies, and the immunohistochemical characterisation of tumours for different metabolic, immune and tumour markers. The final step is the validation in human samples from healthy donors or patients using PBMCs or tumour tissue arrays.





## SCIENTIFIC CONTEXT

Cancer can be defined as the uncontrolled growth and division of cells, leading to tumour formation, invasion, and metastases. Unlike normal cells that require growth factor signals, tumour cells often have mutations that result in constitutively active ('always on') signalling pathways that drive aberrant cell growth and division. In order to fulfil the high nutrient demand required for their continuous growth, tumour cells have reprogrammed their basal metabolism from an oxidative to a more glycolytic/anabolic one, even in the presence of oxygen. Otto Warburg proposed in the early XX century that, 'this altered metabolic state was the underlying cause for cancer' (Warburg 1956). The past decade has been a period of very active research in the area of tumour metabolic reprograming, and major molecular mechanisms involved in the process have been identified and characterised. It was found that both oncogenes (Ras, Myc) and tumour suppressor genes (p53, RB, LKB1) impart an altered metabolic phenotype in cancer cells through the regulation of genes involved in central metabolic pathways such as glycolysis, fatty acid metabolism, oxidative phosphorylation, nucleotide synthesis and the one carbon pool (reviewed by Gilmour & Velasco, 2017). All these alterations have led tumours to rely heavily on specific metabolic pathways to obtain their energy, while using other pathways to grow in order to give tumour cells a growth advantage. This situation may leave tumour cells in a frail position under certain treatments or circumstances, while normal cells may be able to compensate, adapt and survive. Our laboratory is searching for this metabolic weakness in order to stop tumour growth.

Furthermore, the high requirements of nutrients and other soluble factors as well as the release of metabolites with immunosuppressive properties, together with the hypoxic conditions found in tumours, create a 'non-friendly' microenvironment for an anti-tumour immune surveillance, while facilitating the growth of other tumour-promoting cells such as stroma and myeloid cells (FIGURE A, B). Thus, the mechanistic understanding of cancer metabolism has led to renew interest in developing therapeutics that target key enzymes involved in this process. Checkpoint-blockade immunotherapy has been one of the most exciting advances made in cancer treatment in recent years. Metabolic interplay in the local microenvironment can mediate T cell differentiation and function. 'Checkpoint-blockade' antibodies can also influence cellular metabolism. Finally, recent clinical trials have shown that combination immunotherapy, based on immune checkpoints blockade and targeted and non-targeted therapies, provides even higher response rates than either approach alone. Several clinical trials are currently using this approach, however, not all patients respond to immunotherapy and it is, therefore, necessary to determine which patients would be good candidates for the treatment. It has been found that an inflammatory tumour microenvironment – 'hot' tumours – greatly increases patient survival. One of the objectives of our laboratory has been to identify, and characterise the expression of novel and known tumour markers that may enable a better patient stratification for future therapies. This approach has shown that, in addition to the levels of expression of an immunotherapy target, the type of cells that express the marker may also be a feature to consider. ■

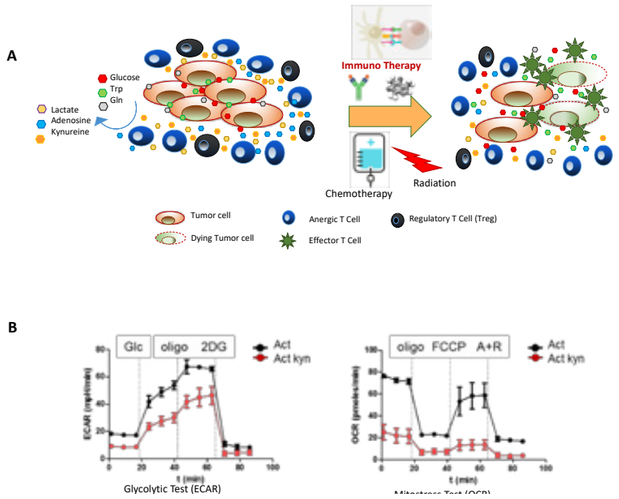


**Figure** Targeting cancer metabolic immune suppression. (**A**) Tumour cells produce a battery of immunosuppressive metabolites such as lactic acid, kynurenine or adenosine that result in an anergic T cell phenotype, while consuming key metabolites such as glucose or tryptophan necessary for a proper Teff ($CD8^+$) activity. As a result, T cells are metabolically incapable of mounting an antitumour immune response. Metabolic regulation, together with immunotherapy and other classical therapies (radiation, chemotherapy) of the tumour and/or the tumour microenvironment, would diminish the production of immune suppressive metabolites and increase the levels of metabolites such as glucose, or the tryptophan necessary for a proper anti-tumour T cell response. (**B**) Extracellular flux analysis for the acidification rate (glycolytic test) and $O_2$ consumption OCR (mitochondrial test). Fully active effector T cells require an activated glycolytic and an oxidative metabolism in order to synthesize cytokines and other molecules necessary for their cytotoxic activity. Immune suppressive metabolites, like kynurenine, suppress the metabolic activity of effector T cells inhibiting their cytotoxic activity.

# CNIO - LILLY EPIGENETICS SECTION

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## SCOPE OF THE CNIO - ELI LILLY PARTNERSHIP

Eli Lilly and CNIO were collaborating on the identification and validation of novel targets in cancer epigenetics. Our Section was funded through a research contract with Eli Lilly and focuses on the identification of small molecular weight molecules able to modulate the epigenome of malignant cells and ultimately block the growth and spread of tumours. Potential targets were validated *in vitro* and *in vivo* using animal models developed at the CNIO. Furthermore, we set up biochemical and cell-based assays with the aim of understanding the mechanism of action of such targets at the molecular level (FIGURE).

## SCIENTIFIC CONTEXT

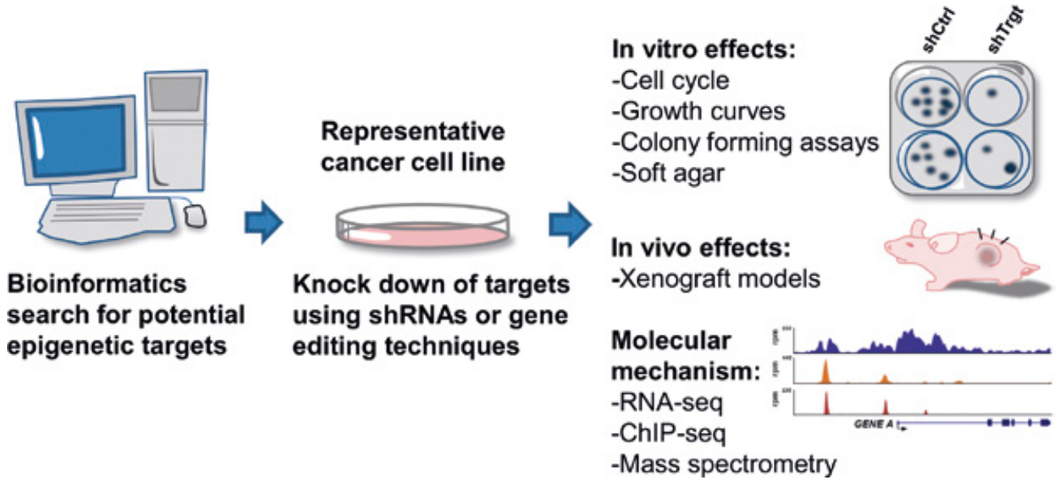


**Figure** *In vivo* and *in vitro* strategies for target validation.

Recent studies have shown that the alterations that take place in cancer cells not only occur at the DNA sequence but also at the level of the epigenome. Eukaryotic DNA is wrapped around histone proteins to constitute chromatin, which plays fundamental structural and regulatory roles. The epigenome consists of chemical changes in both DNA and histones that can be inherited through cell division and are controlled by the action of a large set of epigenetic regulators that possess enzymatic activity. Ultimately, DNA and histone modifications control the level of chromatin condensation, which in turn regulates the accessibility of transcription factors to the chromatin and, therefore, gene expression.

During the past few years several studies, including our own, have suggested that the deregulation of the chromatin-modifying machineries can lead to aberrant gene expression causing cancer and other human diseases. The epigenome is regulated in a highly dynamic fashion by the coordinated action of regulators able to write, erase and read histone and DNA modifications. Thus, contrary to genetic mutations, epigenetic aberrations can be reversed through the targeting of the appropriate epigenetic regulators. Indeed, drugs targeting DNA methyltransferases and histone deacetylases have successfully demonstrated anticancer properties and are currently used in the clinic. Therefore, identifying the molecular function of critical epigenetic regulators and their complex relationship with the cancer epigenome (FIGURE), as well as the development of small molecular inhibitors of their activities holds great promise for the therapeutics of cancer. ■

### PUBLICATIONS

- Garcia-Carpizo v, Ruiz-Llorente S, Sarmentero J, Graña-Castro O, Pisano DG, Barrero MJ (2018). CREBBP/EP300 bromodomains are critical to sustain the GATA1/MYC regulatory axis in proliferation. *Epigenetics Chromatin* 11, 30.
- Garcia-Carpizo v, Ruiz-Llorente S, Sarmentero J, Barrero MJ (2018). Therapeutic potential of TAF1 bromodomains for cancer treatment. *bioRxiv*. doi: https://doi.org/10.1101/394254.