Version Française

English version

INTEGRATED RESEARCH PROGRAM 1

LEADERS

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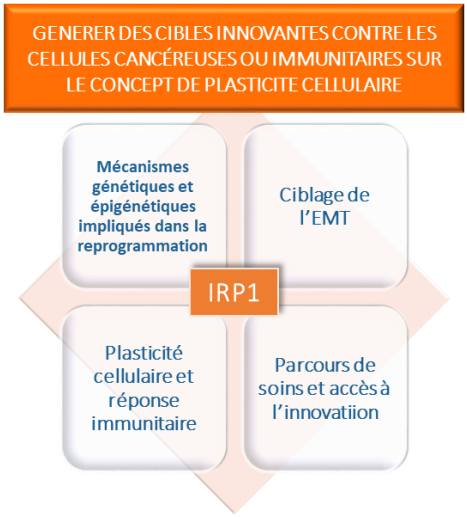
IRP1 : GENERER DES CIBLES INNOVANTES CONTRE LES CELLULES CANCÉREUSES OU IMMUNITAIRES SUR LE CONCEPT DE PLASTICITE CELLULAIRE



Par le biais de diverses approches dans des modèles différents, cet IRP est dédié à la découverte de nouveaux gènes ou protéines qui démontrent un rôle moteur dans des mécanismes de plasticité, et dont la modulation favorise la mort cellulaire dans les cellules cancéreuses ou sensibilise les cellules du système immunitaires.

Trois axes majeurs sont déclinés pour répondre à ces objectifs :

- Les mécanismes de reprogrammation liés à la plasticité
- Le ciblage de l'EMT (Transition épithélio-mésenchymateuse)
- La plasticité des cellules du système immunitaire

Le précédent SIRIC a fortement contribué au programme de profilage moléculaire régional **ProFILER** et sur cette dynamique, de nouveaux projets vont continuer de contribuer à la caractérisation moléculaire de tumeurs rares par le biais d'approches plus globales, avec de l'exome et du transcriptome.

Dans cet IRP, les questions de sciences humaines et sociales portent sur l'accès aux soins et à l'innovation, et plus précisément sur les inégalités territoriales ainsi que le parcours global du patient, en exploitant aussi le réseau européen EURACAN (Dir JY Blay) sur le plan politique et institutionnel.

IRP1 : UNDERSTANDING CELL PLASTICITY TO IDENTIFY INNOVATIVE CANCER CELL AND IMMUNE CELLS TARGETS

The IRP1 is divided into 4 axis, as follows :

- **AXIS 1. Genetic drivers and epigenetic reprogramming in cancer cell plasticity – Identifying genomic alterations and epigenetic modifiers ("epidrivers")**
- **AXIS 2. Targeting EMT-driven cancer cell plasticity**
- **AXIS 3. Cell plasticity and immune responses**
- **AXIS 4. Patient trajectories, networks and accessibility to innovative treatments**

Intra-tumoral heterogeneity is a real challenge for precision medicine. To address this question, different approaches are being developped in order to identify new genetic or epigenetic targets involved in cancer cell plasticity. **GENETIC TARGETS**: ProFILER, the first molecular profiling clinical trial set up and supported by the first SIRIC has yielded a large amount of data available to perform datamining. Indeed, 3210 patients could benefit from the molecular characterization of their tumor (using a panel of 74 genes), among which 757 patients could have a recommandation of treatment. This first step led to ProFILER02, with the support of Roche Pharma France, which is dedicated to assess the benefit of a larger panel (Panel FOne FoundationOne®, 315 gènes) versus the acedemic panel used in ProFILER (74 genes). The identification of new genetic or epigenetic should should lead to drug developpement. Indeed, the C3D laboratory (CENTER FOR DRUG DISCOVERY AND DEVELOPMENT) is a dedicated structure able to perform the screening of a large number of drugs. The pre-clinical evaluation is also possible on site, giving the best environment conditions for innovation. The well-know and described plasticity mechanism is the epithelial-to-mesenchymal transition, aslo called EMT. The laboratory of Alain Puisieux (CRCL) has published key findings on the role of embryonic transcription factors in this process, as well as the capacity of stemness induced by those transcription factors can protect cells from chromosomal instability increasing stem cells' intrinsic susceptibility to malignant transformation. Based on this strong expertise and well characterized cellular models, EMT associated biomarkers will be studies to generate EMT-targeting drugs. Cell plasticity and consequent escape mechanisms are not only true for cancer cells but also for immune cells. Antibodies against immune check points (PD1 or CTLA4) demonstrate remarkable efficiency in several major types of advanced cancers such as melanoma, lung, kidney, bladder and head and neck carcinomas. Response rates range from 15% to 40%. However, these promising immunotherapies have limitations: i) only 15% to 50% of patients respond to treatment in susceptible diseases, ii) certain cancer types are poorly sensitive to ICP immunotherapies, iii) responder patients often relapse because their tumor acquires resistance mechanisms, iv) toxicities are frequent, vi) the cost of these treatments is very high. Response to treatment is also known to be dependant on the infiltration of immune cells, such as T-Cells. The objectives are to decipher the consequences of tumor cell plasticity on immune recognition and immune escape and to characterize immune cell plasticity during tumor progression and identify targets to restore anti-tumor immunity. The program will, in first place, focus on breast, gynecological, and lung cancers, melanomas, lymphomas mesothelioma and sarcoma.

Integrated social sciences and humanities projects

Due to the emergence of various new targeted therapies, a number of sociological questions arise regarding their accessibility to the general population. Therefore, three axis will allow to investigate: – the access, – the impact on patient trajectories, – the difference in France and in Europe. Unique active networks, such as the sarcoma network or the European Reference Network (EURACAN), will be used to assess the various questions of this IRP1 regarding access to innovation.