Description of research areas in the Plan Cancer

Within the Plan Cancer research strategy, we propose to focus on such incurable and treatment-resistant cancers. Based on the progress in “omic” technologies and bioinformatics, personalized treatments will most likely have a future role in the treatment of “incurable cancers” defined by their poor prognosis and drug resistance.

In view of the current clinical needs and opportunities, and the existing research landscape in Luxembourg, a strong focus should be on the following three research axes:

i) Cancer Immunology,
ii) Tumour Resistance
iii) Neuro-Oncology.

A major challenge will be the development of new treatment strategies for recurrent disease and clinical tests for treatment guidance and risk stratification. Future research activities will therefore bring new solutions to clinicians for better treatment and patient management.

**Cancer Immunology**

1. **Understanding why cancer immunotherapy based on immune checkpoint inhibitors does not benefit all cancer patients.**
   - Understanding the molecular mechanisms underlying the expression of immune checkpoint inhibitors and those regulating the infiltration of immune cells into the tumour bed.
   - Attention should be paid to the complexity of the tumour ecosystem and the impact of the tumour microenvironment in regulating anti-tumour immunity.
   - Developing a more comprehensive understanding of the tumour heterogeneity and how heterogeneous tumours develop resistance to therapies in order to expand our understanding of treatment responses.

2. **Identification of biomarkers to monitor treatment and predict response to immune checkpoint inhibitors.**
   - Identification of reliable blood-based biomarkers to predict treatment outcome of immune checkpoint inhibitors and stratify responders versus non-responders could be relevant to optimize the use of cancer immunotherapies in the clinic.

3. **Identification of novel therapeutic targets**
   - Identification of adaptive mechanisms leading to the emergence of resistant tumour cells able to outmanoeuvre an effective immune response and escape from immune surveillance as a basis to develop novel therapeutic targets to improve current cancer immunotherapeutic approaches based on immune checkpoint inhibitors.
Tumour Resistance Mechanisms

Understanding the molecular mechanisms that govern resistance to treatment:

1. Identify and characterize the molecular mechanisms that confer resistance to first line treatments. Amongst the mechanisms that need to be considered in priority are mutations/epigenomic changes, clonal selection, as well as phenotypic and metabolic adaptations to a changing microenvironment.

2. Understanding the changes in the epigenetic landscape (i.e.; alterations in DNA methylation, histone modifications, non-coding RNAs) associated with treatment resistance may provide novel anticancer therapeutic strategies, whereas identifying the DNA repair pathways that operate to promote tumour resistance may uncover novel strategies aiming at sensitizing tumours to first-line genotoxics or eradicating recurrences through the inhibition of specific DNA repair molecules.

3. Identify predictive biomarkers that will allow better patient stratification and selection for first line treatment\(^1\)\(^ 2\)\(^ 3\), and scalable biomarkers of treatment response/resistance that will allow monitoring of patients.

4. Identify novel agents and approaches, including combination and/or targeted treatment approaches to overcome the resistance phenomena observed with current therapeutic strategies.

Neuro-Oncology

1. **Targeting the glioma invasion compartments**
   - Develop innovative screening approaches for new drug targets, the consideration of tumour-host interactions in cell invasion, as well as the development of novel imaging protocols (MRI) to detect and visualize infiltrating tumour cells.

2. **Targeted radiotherapy and immune system modulation**
   - Develop a better understanding of the interaction between radiotherapy and the immune system provides enormous potential for brain tumour patients, including those with brain metastases.

3. **Development of novel experimental therapies**
   - Develop innovative treatment approaches based e.g. on oncolytic viruses and immunotherapies that could be applied alone or in combination with emerging targeted therapies focusing on tumour metabolism and tumour angiogenesis.

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