Translation research

The term “translational research” describes research that has as its objective the direct transfer of laboratory-based experimental knowledge to clinical practice. It is a complex concept that has a great diversity of expression. The ideal example is that of new anti-cancer therapies (and against other human diseases, in general) for use by clinicians which could increase specificity and efficacy of the treatment. This depends on a more profound knowledge of the molecular bases of not only the disease but also of the therapeutic targets and of the effects of treatment.

Translational research is a very wide term that requires the integration of a multitude of complementary aspects such as the assimilation of new knowledge, the imaginative design of new therapies and the application of new methodologies. A fundamental aspect is the identification of the genes that regulate each of the steps in the carcinogenic process; a knowledge that is encoded within the term “genomics” and the unlocking of which can lead to the identification and evaluation of new therapeutic targets. Some examples are the growth factors and their receptors, the GTPases and their modulators, the regulators of intra-cellular kinases and phosphatases, transcription factors, and the proteins related to adhesion, to metastases and to angiogenesis. Once a new therapeutic target is identified and validated, a complex set of activities need to be implemented to make the therapy more effective and appropriate for each particular case. These include the generation of antibodies, design of synthetic inhibitor/stimulator molecules, creation of vaccines etc. Examples of pharmaceutical preparations that have been generated recently, and which can serve as a successful model for such a process of “translational” investigation include: Herceptin (a monoclonal antibody against HER2) which is effective against breast tumours that over-express the HER2 receptor; Gleevec (a synthetic molecule that inhibits the kinases Bcr-Abl, c-Kit and PDGFR) which is effective against chronic myeloid leukaemia and gastrointestinal tumours; C225 (a monoclonal antibody against the EGF receptor); and Iressa (a selective inhibitor of the tyrosine kinase activity) which is active against the EGF receptor in various solid tumours such as colon, non-small cell lung cancer (NSCLC), head & neck, ovary and prostate. From this “translational” research, it is estimated that more than 400

compounds have been identified using the strategies of identification and evaluation similar to those described for Herceptin, Gleevec, C225 and Iressa, and which are currently in different phases of pre-clinical or clinical trials. These agents will probably constitute the new therapeutic arsenal in the fight against cancer in the near future and is, perhaps, the best known aspect of “translational” research. Similarly, the identification of agents that induce or are precursors of specific types of cancers, has contributed to the design of campaigns for prevention that exert a powerful driving force in changing the life-style habits in populations. Over the past few years there have been 3 main fronts that have produced important results. Firstly, the isolation of mutagenic agents directly from tobacco and the identification of their effects on certain genes has added weight to anti-smoking campaigns and the results are highly significant with respect to the diminution in the incidence of tumours related to the consumption of tobacco, such as lung cancer. The results are particularly impressive in those countries with aggressive anti-smoking campaigns. Secondly, the wealth of information that has been collected with respect to the injurious effects of ultra-violet radiation resulting from exposure to excessive sunlight is being actively disseminated. The results will translate, over the next few years, into a significant reduction in the incidence of melanomas. Thirdly, several campaigns are in place for the introduction of vaccination programs against HPV, HBV and HCV viral infection. In populations exposed to the risk of infection, this should result in a decrease in the incidence of tumours of the cervix, head & neck, and liver since these tumours are known to be associated with these viral infections.

“Translational” research can, as well, define precise bio-markers for improved detection, diagnosis, prognosis and the monitoring of tumour processes, including response to therapy. This information, encoded in the so called “oncogenomics”, is causing a reclassification of tumour types based on their molecular characteristics rather than the traditional classification which was based on the histological origin of the tumour cells. These new tools help the oncologist by not only making the new information on the tumour process available but also in facilitating the design of

therapies that can be tailored to the individual's needs as well as with respect to functional characteristics of the tumour.

Similarly, technological advances are having an extraordinary influence on "translational" research. Of outstanding interest are the techniques of "microarrays" for evaluating gene expression, "proteomics" or the analysis of protein product expression and modifications, and the techniques of molecular imaging. These are only a few of the examples of the advances in biomedical research and the impact they will have on the future development of new technologies. These techniques are causing a revolution in the acquisition and processing of the data that are becoming increasingly necessary when making the decision on the most appropriate anti-tumour treatment and the personalization of the therapeutic process. The technological advances in "pharmaco-genetics" (defining possible adverse responses) and "pharmaco-genomics" (defining the most appropriate therapy and response-to-treatment follow-up) provide information on the real efficacy of treatment and response on an individual patient basis. This availability of information on tumour type and individual response to treatment is very necessary if the net result is to be a better prospect of a cure. Similarly, systems need to be increasingly precise and efficient in the administration of radio-therapeutic drugs if higher rates of cure are to be achieved. The use of radio-sensitisers and radio-protectors make a treatment more effective against

tumour tissue while adjacent normal tissue remains relatively unaffected.

The information that is generated daily in both basic clinical and experimental research laboratories, together with their improved management, have an influence on the lifestyle of the patients as a function of their genetic characteristics. Together, these suggest guidelines for the management of cancer as a chronic disease and, as such, comparable to other diseases. This concept may be more easily assimilated by society but because new mutations can occur and accumulate and since resistance to treatments can develop (a property that is inherent in tumour cells), to consider cancer merely as a chronic disease is a concept that is not without risk. Other avenues that need to be explored are the possibilities of totally eradicating all tumour cells of an organism, but this will only become an achievable option when we have learnt to manage, with greater efficiency, the specific responses of tumour relative to normal cells.

The human imagination has no boundaries and, without doubt, the vast amount of new information generated by "translational" research will pave the way for the design of specific, very selective, and efficacious treatments against each of the >100 diseases that we have come to know as cancer.

Dr. Juan Carlos Lacal
Associate Editor