The Importance of Translational Research for Cancer Centers

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It is obvious and most likely does not need any further explanation that Cancer Centers have been established in order to contribute to and to improve current modalities in cancer prevention, risk assessment, diagnosis and therapy. In my personal opinion this has led to significant achievements during the past decades, although there is still a long way to go. Moreover aid in psychosocial aspects of cancer patients and in cancer rehabilitation may as well be included. I am not going to discuss the latter two aspects here.

Presently the terms „translational research“ or research „from the bench to the bedside“ and vice versa became partially political and increasingly influence orientation and research directions in Research Centers. What are the major reasons for these developments?

With the advent of molecular biology, cloning and amplifying procedures for specific nucleic acids, almost unexpectedly, previously basic research without visible practical application, suddenly became available initially for diagnostic and subsequently for preventive and in the future hopefully increasingly also for therapeutic purposes.

At our Center, for instance, the work of Werner Franke and his group, in the early phase entirely devoted to the characterization of cytokeratins, led to the identification and characterization of a family of related proteins, specifically expressed in specific locations. It very quickly turned out that many of these proteins prove to be useful tools in the histodiagnosis of cancer. Some of them emerge as useful markers in metastatic tissue in patients with unknown primaries.

We experience in these days an explosion of diagnostic markers, to a large degree based on molecular cytogenetics, identifying specific fusion genes in human leukemias and lymphomas, as well as in several solid cancers, the modification of oncogenes and tumor suppressor genes, also as indicators of germline genetic changes and of an inherited risk for specific cancer types. Molecular diagnostics dramatically increased in power and resolution with the advent of the PCR technology.

Initially, novel diagnostic approaches comparatively rapidly find their way into practical application. They do not require the same lengthy procedural steps before being brought directly to the patient. Of course, the risk of their failure should not have the same consequences as a harmful therapy. With the availability of the human genome sequences it is very likely that molecular diagnostics will play an even more important role in the future. I am sure that none of the existing Cancer Centers wishes to be excluded from these developments.

The identification of a cancer risk factors frequently has immediate impact on cancer prevention. Finding of such factors, be them chemical, physical or microbial, may quickly result in their removal from the respective environment. This accounts in particular for occupational risk factors, e.g. nitrosamines in rubber factories, asbestos used for insulation, pharmaceuticals, and many others. Usually companies react very fast, since the removal of the culprit avoids ostracism by the consumers.

The inefficiency of translating some of these results into practice in assessing cancer risk factors is best exemplified by the relative ineffectiveness of antitobacco campaigns in many of our countries, particularly there where a significant part of the state income is derived from the taxation of tobacco products.

The identification of microbial agents as risk factors for specific types of cancers did lead to fast consequences in the case of the role of Helicobacter pylori in gastric cancer and gastric lymphoma. Effective modes of treatment had been available already at that period of time and in can be anticipated that at least in those countries where this treatment is affordable gastric cancer probably will show an accelerated decline. Hepatitis B virus (HBV) vaccines had been available even before this virus was identified as a major risk factor for hepatocellular carcinomas. The enforced application of this vaccine to all newborn children in Taiwan since 1986 resulted already by now in a recognizable trend of liver cancer reduction occurring there already in children of 10 years and older. Since hepatocellular carcinomas linked to HBV infections play a major role in the cancer incidence, particularly in South East Asia and Africa, the preventive potential of the HBV vaccine is substantial.

In the case of papillomavirus infections and cancer of the cervix the transfer of laboratory results to practical applications, besides a very limited diagnostic application, takes approximately 20 years. The development of vaccines is well on its way and, as judged from animal experimentation and first phase clinical trials, bears the promise of success. A global application of this vaccine, if as successful as anticipated, could theoretically prevent about 12% of the present cancer incidence in women. This calculation also includes other cancers linked to anogenital papillomavirus infections. Theoretically it would mean that more than 500 000 cancer cases in women could be prevented annually by successful vaccination programs. Why does it take probably slightly more than 20 years from the discovery of the causative agents to the application of a preventive vaccine? The answer is not too difficult to provide: first of all it took several years before the clinicians were convinced that HPV types really cause cervical and other cancers. In fact, the German gynecologists for instance had their first keynote lecture on HPV and anogenital cancer in a national meeting in 1996, 13 years after the discovery of the viruses involved. This may not be too
surprising, since the most common prototypes were discovered in Germany, and like the prophets in biblical times, you do not believe what is invented in your neighborhood. In some other countries, particularly here in the United States the situation was different. This resulted here in earlier acceptance of laboratory data.

A second reason, closely related to the first one, also contributed to the delay. I remember when we in 1984 presented our data to a pharmaceutical company, at that time heavily engaged in vaccine production, and proposed a collaboration for the development of a vaccine, the response came about 4 weeks later: no, there was no interest since there would exist many other urgent problems and a quick market analysis did not look promising. Fortunately the situation changed today as did the market analyses. But an early movement and active engagement of industry in this development probably would have led to an earlier application of the vaccine by a couple of years and may have prevented cancer in possibly more than a million of women. Maybe this is a good example for a gap between laboratory research and industrial production, certainly in part due to the lack of experience on both sides. In fact, such experiences should emphasize the need for a dose collaboration.

In cancer therapy the interest of pharmaceutical companies is visible everywhere. The development of targeted chemotherapy appears to enter first exciting phases with new treatment regimens in acute promyelocytic leukemias and chronic myelogenous leukemias. The increasing understanding of signaling pathways and the detailed analysis of modified proteins in cancer cells clearly offer new avenues for cancer treatment and for interactions between Research Centers and Industry.

The use of therapeutic vaccines against specific cancers, mainly melanomas and kidney cancers, established in a way a kind of renaissance of older concepts of immunotherapy. Present approaches are mainly based on the use of activated dendritic cells and from the beginning characterized as translational research, even initiated in dose collaboration with the respective patients. In contrast, however, to other therapeutic concepts, these attempts aim at an individualized cancer therapy, they may thus be less attractive for some of the large pharmaceutical companies.

It is interesting to note how long it took to develop therapeutically active monoclonal antibodies. The discovery of monoclonal antibodies with selective binding specificity was published by Köhler and Milstein in 1975. The initial hopes for therapeutic use soon turned into frustrations, since numerous obstacles seemed to block the way to use these constructs for cancer therapy. It is almost a surprise that approximately 25 years after their discovery reports on successful clinical applications are emerging: this relates to specific B cell lymphomas and a subset of breast cancers and to a limited degree also to the prevention of metastatic spreading of some colorectal cancers. Here the persistence of some researchers was the key to success.

It seems that we encounter presently a somewhat analogous situation in the clinical application of gene therapy. Numerous clinical trials had been initiated and are at present running - without significant success, at least as far cancer treatment is concerned. The willingness to transfer clinical results into practical applications is quite pronounced, yet, the absence of convincing clinical data on the one hand and required procedures for licensing a new drug on the other render it likely that much more time will elapse prior to entry of gene therapy as an established treatment protocol.

I did cover thus far exclusively examples derived from developments in translational research in molecular medicine, immunology and virology and omitted a large area of other directions. But whereas the previously discussed topics developed more or less only during the past 25 years, novel techniques in cancer treatment, in surgery and radiation therapy, in screening procedures, in search for serological cancer markers and others have a much longer history and in part date back to the turn of the past century. Time does not permit me to discuss these in more detail. Obviously these topics continue to play the dominant role, particularly in cancer treatment regimens and will almost certainly do so in the forthcoming decade.

Particularly the developments in biotechnology and molecular medicine created a sudden enthusiasm among politicians for translational research. It emerged like a magic formula solving economic problems in countries with a morbid economy. The pressure is growing visibly in Europe and deflection in part from requirements in basic research. In addition, the willingness of most scientist to go where the money is, may create in turn a problem. Is it justified to put the emphasis in Cancer Centers mainly to the translational perspective? To which extent and how should it be linked to Hospitals or to the pharmaceutical industry?

The obvious question resulting from this discussion is the following: are our Cancer Centers sufficiently equipped and ready for an active role in translational research? Many of them are either devoted entirely to clinical studies or more oriented towards basic research. Is there a role for basic research in the future development of Cancer Centers? To which extent and how should it be linked to Hospitals or to the pharmaceutical industry?

My personal view is readily expressed: indeed we need basic research in our Cancer Centers as an element of creativity and originality. The major discoveries related to our understanding of cancer, the molecular techniques in risk assessment, in cancer prevention, diagnosis and therapy all rooted in discoveries that were not necessarily linked to cancer research. On the other hand, most of the basic research activities in Cancer Centers are application oriented and frequently determined by clinical interests.

As pointed out in the beginning, translational research to a substantial degree originated from the applicability of molecular data to the various fields of cancer intervention. For many of the experimentalists it has been a learning process to follow an active patenting policy, to create technology transfer offices and to establish their own companies, developing business plans, consider the marketing of
their projected product, and actually sell them effectively. In my experience the mentality of the biologists and of other researches active in this field is in a stage of gradual transformation and transition, fermented by the rapid developments in molecular medicine that seems to be desirable - to a large degree. I am personally a bit reluctant to accept an overwhelming commercial orientation of thinking among our young researchers and clearly wish to find some among them who are mainly triggered by their curiosity and by questioning even well established facts. Fortunately, some of them still exist and hopefully this will continue in the future.

For the sake of our cancer patients we desperately need a fast translation of research results into clinical practice as soon as their beneficial effect becomes apparent. Every cancer center is obliged to contribute to these aspects. We should however not forget that a kind of blind activism in this direction may reduce attempts to fully understand the nature of cancer and of individual cancer types and to identify their respective risk factors. This still remains a domain of basic research where most of the potential for an effective cancer prevention lies. It must be our primary aim to prevent cancer occurrence, even be it solely for the sake of our children and grandchildren, effective prevention is clearly better than the most effective treatment. And here we need both a dose interaction between the basic researcher and those who are capable to translate those results into practical application.