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Professor Alexander Eggermont, general director of Gustave Roussy, gives insights into the transformation of the Hospital under his ten-year leadership mandate. He also explains the rationale behind creating Cancer Core Europe, a collaborative platform of Europe's seven leading cancer institutes.

What have been your priorities since we last interviewed you, four years ago?

My main objective has been the continuation of transforming Gustave Roussy from a comprehensive cancer centre to *the* comprehensive cancer centre dedicated to innovation. In that context, we have created a new drug development entity called the Department of Therapeutic Innovation and Early Trials (DITEP), which is the only division of its kind in Europe. It is a fully-fledged department with more than 200 people working on 125 early clinical trials, 67 of which are in the area of immuno-therapy. When I arrived here back in 2010, we only had one Phase I immuno-therapy clinical trial, so I am quite proud of this achievement.

The transformation had to be accompanied by a number of additional measures, as we required dedicated labs for translational research. We have thus built a new 6000m^2 research facility with 20 laboratories and one floor completely devoted to the interaction with our early clinical trial program. Both elements are essential to being fit-for-purpose and to fashion a new culture of total

integration, all the way from basic research to translational research to clinical application. Our system brings between 3500 and 4000 patients into clinical trials every year, which makes it the largest such program in Europe and for early clinical trials one of the top 5 programs worldwide. This also means that we also hold the status of being a national centre of excellence.

How do you go about attracting the calibre of scientific personnel that you require?

It is essential to go all the way and put in place a really comprehensive set of capabilities if we genuinely aspire to become *the* leading institute for access to innovative cancer therapies. This is also crucial for being able to keep our clinicians happy by providing top-notch clinical platforms dedicated to innovation. Our role is to develop new forms of indications and it is our mission to dedicate ourselves to activities that not every institute can perform. I believe it is essential to provide great infrastructure in the fields of surgery (a robot dedicated to the development of new indications), radiotherapy and nuclear medicine, and molecular diagnostics and immunoprofiling. so as to provide unique value to our specialists, who also enjoy substantial free time for performing their own research.

The best pathway to sourcing and retention of high-level experts is by delivering up a stimulating and structurally complete ecosystem. I am convinced that this the underlying reason why we consistently retain so many here at Gustave Roussy, despite pay scales being more enticing in certain other markets. We can only do this, though, so long as we continue to find the requisite funding to be able to ensure these conditions.

How are you able to ensure this type of funding?

We have the Gustave Roussy foundation as well as package deals with industry for entire projects, which includes support for translational research. It is a fundamental function of the institute to source financing and, in many people’s minds, it has almost become taken for granted that funding will always be provided. It is not an easy task, however, and we have to go after it all the time. I can assure you that substantial work goes on behind the scenes to ensure that the money keeps rolling in.

Which other infrastructural projects are being planned?

Within a couple of months, we will launch a preclinical cancer research building, called PRECAN, as part of a project worth between 40 and 50mn Euros (45-56mn USD). This will enable the creation of the foremost preclinical platform for cancer in Europe, including an MRS clinic, an imaging floor and a space for start-ups. The rationale behind having our own start-up floor within the institute is to ultimately develop into a bio park.

Integrating young companies is the keystone of the attractiveness of the bio park that we envision. If this is not being done under a single roof, there will be too many stakeholders and we will risk ending up with an operating environment experiencing many hiccups, and one that cannot easily be steered. It is an ongoing theme within healthcare to bring more and more people and decision-makers to the table to the point, where this tendency now endangers core capabilities by slowing down processes.

All too often the consequence of too many stakeholders is chronic inertia and squandered opportunities. For me, as a surgeon, it is very difficult to work with this type of culture that loses focus and depletes the willpower to move and deliver fast. Having an unnecessary number of actors can also impede the funding process, as it is easier to have a small steering committee with expertise and centralized decision-making power when negotiating with venture capitalists. While I have two more years left of my ten-year mandate to finish the internal transformation of Gustave Roussy, it has to be understood that the outside world cannot be changed or transformed in that way so we obviously have to be realistic in our expectations and work within the parameters that we find ourselves.

Do you encounter a similar mindset when dealing with the six other European institutions that today form “Cancer Core Europe”?

When looking back at historic European frameworks on cancer, such as the European platform for translational cancer research (EUROCAN Translational Platform), there has been a similar situation blighting many of these platforms. EUROCAN TP was conceived because we had witnessed many gaps, redundancies and duplications across the European medical science research landscape. Initially, we had the idea of establishing a coordinated translational component as part of a broader European network. To implement this proposal, we received the requisite funding but soon found that the necessity to include a whole plethora of disparate partners was making it difficult to advance and make headway. The EUROCAN TP project included some 24 members and 16 work packages. In the end, there was the typical phenomenon of the money being divided up between

the work packages and the corresponding labs. The common result, in these instances, is that the money is spread too thinly and eventually the consortium evaporates without attaining any tangible results. We have witnessed this tendency time and time again.

In response, we started thinking of a leaner, more streamlined structure that could deliver a real European coordinated translational component on cancer. I have a long history at the German Cancer Research Center (DKFZ) at Heidelberg and was also in charge of creating 14 comprehensive cancer centres in Germany. With the DKFS, Gustave Roussy created a bilateral program, as we complement each other's services perfectly. Heidelberg possesses excellent basic research, while we can offer the very best in clinical research. From this collaboration sprung the idea to create Cancer Core Europe, with the principal of only including the very best institutions first to create a legal entity through collaboration. This core includes Cancer Research UK Cambridge Centre, German Cancer Research Center & National Center for Tumor Diseases, Gustave Roussy, Istituto Nazionale dei Tumori de Milano, Karolinska Institutet, Netherlands Cancer Institute and Vall d'Hebron Institute of Oncology.

Today we have developed our own golden standard, with a common read-out system for imaging as well as 450 gene panels, which we can implement at every centre for sequencing. For further translational research development, we will ultimately need to look at each country to initiate the next phase of Cancer Core Europe as we pivot over from "elitist" to "inclusive".

Does this imply that you intend to broaden Cancer Core Europe out in a stepwise manner?

Absolutely. Our model has explicitly been to only work with the best and most high-performance actors initially. There are so many difficulties related to setting up an entity like this that you have to be careful to not destroy the original concept by premature expansion, as rapid enlargement risks diluting the product. There will always be opposition in every country, asking why it is this institution and not theirs to be included. Of course, there are other excellent research institutes in France, Germany and the UK, but including these will be part of the next phase of the sequence and not right away.

We will be expanding at a rate of one institute per country every year for the next four years. Another plan is to open our doors to Eastern Europe, by inviting them to our centres and developing a binome in collaboration with one of our institutes. Gustave Roussy, for instance, is partnering with the International Institute of Molecular and Cell Biology in Warsaw, Poland. The

initiative of the DKFZ with an institute in Greece is even funded by the EU and we will require this kind of support for navigating our expansionist phase.

Currently, Cancer Core Europe is recruiting patients for the largest personalized cancer medicine trial ever done in Europe, called BoB: the basket of baskets trial. We have secured a 20mn Euro funding for this trial from the industry, as they are very supportive of this one portal system we have within the Core.

Many new cancer therapies, like CAR-T, tend to be prohibitively expensive. It is difficult to see the match between increasingly overstretched public healthcare systems and these state-of-the-art, latest generation technologies. What is the way out of this conundrum?

We are in the midst of a structural adjustment that still has to play itself out. The next steps may well be to wait for the American system to break down and fall apart to force a solution. The viability of public health systems is currently being tested as there is a palpable disequilibrium between the escalating price of many therapies and the decreasing ability of the payers to pay up, which necessarily will lead to a major breakdown in the US that should produce the effect of forcibly recalibrating the entire reimbursement model.

In Europe, there is a stringent system in place thanks to the European Medicines Agency (EMA) but also because there is a second layer. We are looking at basic results in every country, to see if the difference is big enough to justify the price and the reimbursement. There is a discussion ongoing on where to put the bar when treatments do not actually cure people.

The Dutch system offers one kind of response by saying that many of these products are not good enough for reimbursement at the moment and need more real-life data to prove the real value accrued. An alternative response can be found in the German system, which reimburses the product, but will then evaluate the real-life value. If the product is not worth the full reimbursement value they make price adaptions and reduce the reimbursement by a certain amount, giving manufacturers the option to withdraw the product from the market or sell at a certain percent. It is a very realistic approach, but what we need for that is to dramatically increase the capability to capture real-life data, to help to conduct a better assessment. Risk sharing linked to continuous performance monitoring is clearly one way to square the circle and take flabbiness and fat out of the system, but that presupposes having an appropriate supporting infrastructure so as to be able to objectively, scientifically and pharmaco-economically track a therapy’s true value impact.

In the past, we have been desperate about any small progress at a ridiculous cost, for instance, the extension of the lifespan of a 75-year-old lung cancer patient by a mere six weeks. Therefore, we should invest heavily in the creation of real-life data, so we can get the best picture possible. This would generate enormous savings and enable us to identify which products are genuinely worth investing in. In many countries, the fog and haziness around health technology assessment are clouding the ability to make informed decisions.

Where is France positioned along this trajectory?

Generics and biosimilars usage is an increasing trend in France. Nevertheless, the country still lags behind countries like the Netherlands, where pharmacies habitually hand out genericized versions routinely and automatically. This brings phenomenal savings to the country's healthcare system. We need to have the pharmacies involved and, for pricing, a common, standardized procedure for all European countries should be identified on how to best reimburse products. There is still a price war on a global scale, so France and Europe need to remain competitive. These trends will also bring down drug prices to a very large degree, however, the volume caused by the high demand for drugs will compensate the price readjustments.

There is no escape from price readjustments in the future as long as we address it rationally and we have the real-life data to back them up. The system will not break down, but we will have to have the right people around to navigate us smoothly through this unavoidable readjustment process. There ultimately needs to be a consensus solution with both industry and government, and payors involved. This will become inevitable as the going gets tough.

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