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The migration and differentiation of a chemist entangled in developmental and cancer biology

An interview with Jean-Paul Thiery

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Jean Paul Thiery started his lifetime dedication to Science as a chemistry student in Strasbourg. He subsequently performed his graduate studies in Giorgio Bernardi's laboratory, where he was involved in projects aiming at elucidating the physico-chemical properties of DNA. He also studied the effects of restriction enzymes and their use as a tool in the elucidation of the structure of the genome.

As a young PhD graduate he joined the laboratory of Gerald Edelman at Rockefeller, where he performed the experiments that led to the discovery of N-CAM. This work laid the foundations for our present knowledge of the Ig superfamily of cell-adhesion molecules. These studies were primarily focused at the elucidation of mechanisms of cell migration and differentiation from the neural crest and instilled in Jean Paul Thiery a life-long interest in developmental biology. Upon his return to France, Jean Paul worked with Nicole Le Douarin in the chick-quail model and fairly soon could establish his own laboratory in Nogent sur Marne. In his own lab he continued to study developmental processes related to the neural crest.

In 1987 he obtained a staff position at the École Normale Supérieure in Paris, where he continued to work in the field of developmental biology, notably the role of cell adhesion in the developing neural crest and the role of extracellular matrix proteins in these processes. It was then that he realised the close similarities between cell migration in the developing embryo and the invasive behaviour of cancer cells.

In this perspective, his decision to join the Curie Institute in 1995 was no surprise. In the division of cell biology at Curie, which he created under Daniel Louvard as director of research of the Curie Institute, his group focused on fundamental processes governing migration of invasive cancer cells. Here he developed the concept of the epithelial-mesenchymal transition during invasion of carcinoma cells, using bladder carcinoma cells as model system.

Jean Paul Thiery was recently nominated director of the new department of translational research at the Curie Institute.

I first met Jean Paul Thiery in the airport at Athens in the middle of the nineties, on the road to a cell pathology course of the EuroCellPath organisation, which was to be held in Ioannina. I myself had worked on cancer cell-extracellular matrix interaction in colon cancer and knew his work well, but I had never had the chance to meet him personally. The course was attended by graduate students in experimental pathology, by pathology residents and by a few big shots. Busy as usual, Jean Paul was just around a couple of days. His talk was on epithelial mesenchymal conversion in invasive bladder cancer cells. A typical Jean Paul show. Bursting with an infectious brand of enthusiasm, he presented a fascinating blend of new findings and smart speculation. I immediately liked his frankness, humour and unconventional way of thinking. In subsequent years we stayed in touch. When Marc Mareel invited me to interview him, I needed no time to reflect on the matter. I immediately liked the idea.

I managed to spend a few very agreeable hours with Jean Paul Thiery in his office in the Curie Institute, right in the academic centre of Paris. I was fortunate to be able to pin him down for a couple of hours. His travels have taken him in the last few weeks from

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Australia to the US and then back to other meetings in Europe. I am on my way back from a two week teaching trip in Cameroun. The contrast between academia in central Africa and the best France has to offer is enormous. From a country where even the simplest of diagnostic or therapeutic needs might not be fulfilled for lack of means..... to a very sophisticated state of the art centre specialised in the treatment of cancer only: a clash of cultures. I have little chance to explain the reason for my visit. As it goes with Jean Paul, he takes off in his presentation of the centre with such an enthusiasm that only a couple of hours later I manage to squeeze in a few of my questions.

Jean Paul, what keeps you faithful to the Curie Institute?

What I am very excited about is what we have accomplished in terms of creating a dynamic and productive research atmosphere. In the eight years since coming to the Curie Institute, I have seen the Institute convert from a poorly visible, marginal operation into a very dynamic research institute, in which I have recently assumed a position as director of a new Department of translational research. My enthusiasm has as much to do with what happened in the past years as with what I plan to do in the years to come. I am fascinated by the rapid advances in our understanding of the biology of cancer and eager to see this knowledge applied to the care of cancer patients.

Sounds exciting indeed but how has the Curie Institute management been able to carry out this conversion?

It has not been easy. The Institute was largely populated with established investigators with tenured positions and little or no incentives to put in the extra effort to attain a level of excellence. In addition, the senior investigators all had their own laboratory, developed their own methods and technical infrastructure without much intra-institutional exchange. As a result, there were many small groups that did not really obtain a critical mass. Most researchers worked in splendid isolation.

One of the first things we did was to change the laboratory structure. Instead of each researcher having his own little “kingdom” we developed open laboratories in which several groups were accommodated and shared the same equipment. With this approach, lateral diffusion of knowledge and skills as well as of ideas was greatly favoured. In addition, core facilities were developed, which have had a major impact on the type of research that developed. We now have an imaging platform which includes electron microscopy, confocal microscopy, laser capture microdissection and two photon microscopy. We have an array facility that works with Affymetrix chips but is also capable of spotting custom chips in-house. We have a proteomics facility that offers cutting edge methods for the development of new cancer markers. Last but not least our intranet has proven very valuable. The Institute has expanded enormously since I came, between 150 and 200 new people have been hired.

Now all this sounds great but how did Curie get this going?

When I got here in the middle of the eighties, the direction of the Institute was rather passive. The staff consisted of solid scientists but not very dynamic nor visionary and without any incentives to be productive or innovative. The Board of Directors of the Institute decided that only a brutal change of approach might revitalise the Institute. They hired Constant Burg as President, who unfortunately passed away untimely in the mid-nineties. Constant Burg had played a key role in the creation of the National Institute for Medical Research (INSERM). He recognised the importance of biomedical research and had as driving force the conviction that patients should profit as rapidly as possible from the results of basic research. He insisted on quality and productivity and did not hesitate to take draconic measures to get done what he deemed essential. He profoundly restructured the Institute, shaking up a good number of scientists of whom the productivity was not up to his standards and creating a new research department with the resources thus liberated and additional seed money. The new research groups were all composed of external recruits. The most important of these was Daniel Louvard, who became the research director. I was also among them, and obtained the resources to create the division of cell biology. Daniel Louvard had his research group in my division, which implied that I was his scientific director and he my administrative director! He was very successful as research director and it has been a great pleasure to work with him. Within a couple of years about 70% of the personnel of the Institute was renewed and on the basis of these principles the Institute prospered.

How is this level of performance maintained?

External review has been one of the key elements in our approach. Each and every member of the Institute is regularly subjected to rigorous evaluation. I have been reviewed some weeks ago and I can tell you, I have been grilled. The Scientific Advisory Board is presided by Howard Green (director of the Department of Cell Biology of Harvard University) and the auditor of my group was David Sabatini and boy, were they tough. They frankly told me that I might be at the top of the list in France, maybe Europe, but that that is not a reason to be complacent.

But is this not perceived as repressive or penalising?

Not really. I cannot deny that I have felt uncomfortable with the evaluation of my group, but do realise that most of the points raised I had thought of before, without taking the trouble to do something about them. But on the whole, the Institute provides an atmosphere which fosters excellence. There is an openness towards multidisciplinarity that favours the development of original new ideas. An example is the presence of Pierre-Gilles de Gennes, a soft matter physicist who got the Nobel prize in 1991 for his research that allowed the development of liquid crystal technology. Incidentally, the Nobel Committee described him as the ‘Newton of the twentieth century’. If you want to know how a cell functions physically, take for example the functioning of molecular motors, the presence of unconventional thinkers opens up new horizons. We are, for example, presently performing experiments trying to understand at the biophysical level what the key parameters are in the establishment of cell adhesion as mediated by the cadherins. To this end we are measuring forces and kinetic constants between individual cadherin molecules. I would never have gotten into this field without de Gennes, with whom we collaborate closely as his present interest concerns the thermodynamics of adhesion, a very complex subject.

Another element is the development of what we call PIC’s *(programmes incitatives de cooperation).* These are multidisciplinary research programmes that are supported by about 150,000 Euro - per project per year. We currently have about 10 of these. They

Fig. 1. Jean-Paul Thiery at an EMBO meeting in 1971 on Port Cros island. *He is the young man sitting on the very left in the front row, in front of his thesis supervisor Giorgio Bernardi. Next to him Piet Borst, the to be, future director of the Netherlands Cancer Institute. Also in the picture, among many other famous scientists, is Francis Crick (second row from the front; third from the right).*

are by definition limited in time: installed for 4 years and renewable only once. But research is regarded as so dynamic that the structures should not become too persistent. Often a PIC starts with a foreign researcher who spends a sabbatical year in the Institute and engages several basic researchers and clinicians in a new project. The PICs present their findings each year in a one day informal symposium which is organised by the Medical and the Research Directors. The PICs have, in spite of the relatively modest budget, had a significant impact on the way we go about the creation of new projects. I should also mention the bio-informatics department that has been created. Along with it we have an extremely useful intranet, which provides as example what we call the 'chimiothèque' a catalogue of all the molecules available in the institute and a platform for datamining, which is essential in the era of the *'omics'* (genomics, transcriptomics and proteomics).

Jean-Paul, are you happy with what you are doing today and does this correspond to what you dreamt of when you were younger?

I enjoy very much what I do nowadays but the evolution of my career has not been something I planned carefully. It has mostly been coincidence, confrontation with intriguing phenomena that captured my attention and my fantasy and the people – great teachers and scientists whom I met and had the opportunity to work with.

Did your family have a strong academic tradition?

I was born into a family without any academic tradition whatsoever. My father was a technician and my mother had worked in small businesses as a salesperson. The most I can say is that there were many teachers in the family. Of my parents my mother was the most "intellectual" and in my education I was mostly supported by her. The children were rather different, which is reflected in what they became. My sister is closest to medicine – she is a nurse. My brother is a chemical engineer but he made it in industry: he constructs chemical plants.

But then, what turned you on to Science?

In secondary school I became aware of my fascination for Science. I liked all the exact sciences but was particularly intrigued by chemistry probably because of my chemistry teacher Ebel for whom I had an immense respect and who guided me towards biochemistry. I immensely enjoyed toying around with chemicals and tubes. I started working on plants during my undergraduate education with Guy Ourisson in Strasbourg, which was mostly organic chemistry. My orientation remained very chemical up to my masters degree.

I got much closer to the life sciences during my graduate training. I ended up in Giorgio Bernardi's lab in Strasbourg, working on physicochemical properties of DNA. At that time I did not

Fig. 2. Jean Paul Tiery (right) congratulated by the well-known French hematologist Jacques Bernard, *on the occasion of the awarding of the French Cancer prize in 1990.*

realise how lucky I was, being selected by the CNRS (Centre National de Recherche Scientifique, the French National Science Foundation) at the age of 21 to pursue further research training close to scientific giants like Jacques Monod! This period was quite extraordinary, working as a young biochemist with Bernardi, who had a medical education but was as adamant as possible about the importance of pure fundamental research.

His approach to biological matter was not very physiological. At that time he basically exploded lymphocytes by centrifugation, in order to be able to study the physico-chemical properties of DNA. It was not until the early seventies, after having obtained my PhD, that I got a little closer to the living cell. After I got my PhD I had realised that I needed to widen my horizon and decided to spend some time in the United States of America. My approach was as bold as befits a youngster of 25. I wrote to about 70 research labs, among which those of David Baltimore, Harold Varmus and Mike Bishop and visited most of them. It was the age of the dawn of retrovirology and I was fascinated by this subject. The result of this expedition was disastrous due to its high success rate: I ended up with 30 job offers and most of them were so exciting that frankly I didn't know what to choose. One of the last labs I passed through was that of Günther Blobel at Rockefeller and I decided to join his team. By chance, however, I had run into Bernie Gilula, who urged me to send my CV also to Gerald Edelman, which I did. And then something extraordinary happened. By return mail I received a plane ticket for New York for an interview the week after. I was so overwhelmed that I did not dare to say no. I still have vivid memories of this trip. When I got there, New York was covered with 2 meters of snow. Edelman was awe inspiring. He grilled me for 3 hours in his office and then insisted that I stay for another week to allow his crew members to continue this torture in the laboratory. I was completely knocked over and decided to join his lab. Incidentally, it was my wife who joined Günther Blobel's lab, and she was closely implicated in the discovery of the signal peptide, for which Blobel got the Nobel prize.

Giorgio Bernardi's laboratory *During his stay in this lab, Jean-Paul Thiery mostly studied physicochemical properties of nucleic acids and the functional organisation of the genome. This was done by what Jean-Paul now calls 'rather crude elementary' methods.* 'We exploded cells by centrifugation' *he recalled,* 'and investigated genomic DNA by density gradient centrifugation'*. Two results stand out from this period. Firstly, the characterisation of highly repetitive (satellite) DNA sequences which contributed to important discoveries in this domain. Secondly, the characterisation of acid desoxyribonucleases, the restriction enzymes, and their use in the analysis of the genome. Again, this work contributed significantly to the development of the field.*

What did you work on in the Edelman laboratory?

The assignment I got was to study cell-cell adhesion. This obviously had to be done in multicellular systems. I barely new what a cell was, let alone a tissue. In 1975, I was sent for three weeks to the Cold Spring Harbour lab to learn tissue culture and it was there that I discovered the cell. With Urs Rutishauser we performed the experiments that led to the discovery of N-CAM.

We had prepared antibodies to the protein fractions that assigned adhesive properties to cells. I realized that we needed to study tissues *in situ* in order to really know what was going on. With the emerging availability of immunohistochemistry, we decided to use immunofluorescence to localize our protein in the chick embryo at a tissue level. To get there we needed to get frozen sections. For me a cell was already a substrate of mind boggling complexity and I knew nothing about tissues. The best thing I could think of was to team up with pathology at the Memorial Sloan Kettering Cancer Institute. I learned the basics of histology there. They also showed me how to use the cryostat and on the sections we obtained we used our antibodies. The result was spectacular: we obtained very specific patterns of immunolocalisation. It was only then that I realised that next to the square meter of bench space I had there was a cryostat – covered with the usual clutter in an overcrowded lab. An instrument in mint condition, unused! Ever since this experience, I have retained an excellent working relationship with pathology and pathologists. At that time, Vakaet in Ghent had studied cell migration during gastrulation in the chicken and quail embryo by electron microscopy and he proposed that the cell junctions he found between the migrating cells might be involved in regulating locomotion. We could show that at these junctions CAM's were expressed. I remember presenting the idea of a family of CAM's decisively involved in embryogenesis at a meeting and being vehemently attacked by Aron Moscona who did not think much of it at that time.

Were you as a chemist easily accepted among embryologists?

That was never a problem. If you have good ideas and quality data you will be respected. But the changes in horizon I went

Jean-Paul Thiery's studies in the Edelman laboratory *form a coherent piece of work which laid the biochemical and cell and developmental biological foundation for our present knowledge of cell adhesion molecules, in particular the cadherins. With Urs Rutishauser, Thiery found a 140 -150 kD protein released by embryonic neural cells in culture, by proteolytic cleavage from the cell surface. Antibodies to this protein prevented cell-cell interactions of retinal and brain cells. The molecule was called cell-adhesion molecule or CAM. It was subsequently found that anti-CAM antibodies inhibited the outgrowth of neurites from cultured embryonal brain cells and also disrupted the morphogenesis of the retina* in vitro*. Using the same antibodies in immunofluorescence experiments, the CAM was localised in the early embryo to the neural plate, the neural tube, the notochord and the somites. In later embryos, neural crest cells and optic and pharyngeal placodes were found to express the protein and also cardiac mesoderm and mesonephric primordium. The remarkable neural association led to the name N-CAM. An additional CAM, the L(iver)-CAM, was strongly expressed on budding endodermal structures including the liver, pancreas, lung, thyroid, parathyroid, thymus and the bursa of Fabricius. L-CAM is presently known as E-cadherin. The latter findings are reported in a landmark 1983 paper in the PNAS, which Jean-Paul understandably considers his favorite and most influential paper. These studies performed on early vertebrate embryos lead to the development of the concept that cell adhesion molecules are the mechanico-chemical links between genes and morphology. They showed that the primary CAM's are not expressed in a cell or tissue specific fashion but are distributed in tissues derived from the three primordial germ layers. Also, they appeared to be expressed on most cells during early development. Their expression later on during morphogenesis and histogenesis was found to be controlled spatially and temporally.*

through in my career were not easy. From hard core chemistry into cell biology and then into the complexity of a developing embryo: it took quite an effort. Compared to those changes the last step, into experimental cancer research, was a lot easier.

When did you enter into the field of developmental biology?

Well, once we new where N-CAM was, the obvious question arose as to the significance of these adhesion molecules for the development of the nervous system. I briefly toyed with the idea to get into *Drosophila* as a model, but then I got an invitation to present a seminar in Nicole Le Douarin's lab. I got along with Nicole very well and we rapidly perceived the potential benefits of our complementarity; she, a world-class experimental embryologist and I with a serious chemical background, and so I decided to team up with her. It was not easy to get started. There was no infrastructure for biochemical studies and I had to start up a lab from scratch. I developed a miniature two-dimensional gel electrophoresis technique, which was applied to the chick-quail neural crest transplant model that had been developed in Nicole's lab, in attempts to isolate new regulators of cell migration during embryogenesis. With Nicole I pursued some studies on regulation of early haematopoiesis in the chick. But I had obtained an independent status in the CNRS system in France and this allowed me to set up my own lab. And that is what I did. I pursued my research initially in the Institute for Embryology in Nogent sur Marne, but in 1987 obtained a position in the Ecole Normale Supérieure in Paris.

These studies further investigated the CAMs and in addition to N-CAM, we characterised L-CAM and Ng-CAM (a neuron-glia adhesion molecule). In addition to structural characterisation of these proteins we studied their function. CAM expression we studied in the chicken and in *Xenopus*. Functional studies were undertaken with dominant negative mutants of cadherin in *Xenopus*. At that time, Don Newgreen had started looking at cell motion *in vitro*, notably the effect of fibronectin on neural crest cells. His approach inspired us to pursue similar studies in the chick-quail model. We studied cell migration in *in vitro* models and realised the importance of intercellular interaction and interaction of the cell with the extracellular matrix. Once you are there, the step to the idea that migrating cancer cells might use the same mechanisms is very close.

Indeed. What made you decide to join the Curie faculty?

My group in the Ecole Normale Superieure did quite well. But the institution did not function as an integrated research institute. There was very little contact between the different research groups. Nothing was shared. What you needed, you had to develop from scratch. I realised that that was not the ideal way to function as an institute. When I got the job offer from Curie, knowing what was going on there in terms of restructuring of the institute, I immediately seized the opportunity. This opportunity also brought me closer to the application of my research in medicine, an aspect that I was more and more enthusiastic about. Incidentally, I still vividly remember the brief meeting I had with the director of the Ecole to announce my decision. He was very upset and really beat me up verbally. But I think he understood why I left.

How did you decide what to develop in terms of your research program at Curie?

Well, the answer will please you. It was again a pathologist that got me going. I ran into Ruy Tchao, an experimental pathologist from Philadelphia, who was working on NTB-II rat bladder carci-

Fig. 3. Jean Paul Thiery (right) with Gerald Edelman (Nobel Prize in Medicine, 1971, middle) and Günther Blobel (Nobel Prize in medicine, 1998, left) *on the occasion of the opening of Thiery's Department of Cell Biology in the Curie Institute.*

noma cells. He had a time-lapse video-microscopy system with which he documented migration of these cells on collagen. I got hooked on these cells and using them, we explored the idea that invasion of carcinoma cells might be accompanied by a transition from an epithelial to a mesenchymal phenotype.

Jean Paul, has your recent appointment as director of a Department of translational research had an important impact on your research program?

Certainly. It may seem strange for a basic researcher but I wanted to get closer to the application of my research in the treatment of cancer patients. That is a fascinating aspect of Curie. We have top notch research labs working very close to clinicians, that have by and large come to recognise the importance of basic research and that are very open to collaboration. So, after my crucial encounters with pathologists, the possibility to work with a surgeon in turn has had an important impact on what we do. Dominique Chopin is a urologist and with him we apply knowledge gained in the lab in the clinics. Our most exciting finding has been that superficial bladder cancers do not normally continue to develop into invasive bladder cancer but constitute a separate entity. These tumours have a mutated FGFR3 and the mutation does not occur in most invasive bladder carcinomas. This is conceptually fascinating but also has a direct impact on the clinical management of superficial bladder cancer. Incidentally, your former collaborator Theo van der Kwast in Rotterdam is closely involved in this work. Apart from the bladder, we explore the possibility to apply concepts from the lab in the clinical management of cervical and breast cancer, using DNA micro-array technology on human tumour samples.

Jean Paul Thiery's laboratory continued to work on cell migration in the context of developmental biology and experimental cancer biology. His laboratory demonstrated the importance of fibronectin for cell migration and the role of the interaction between fibronectin and its integrin receptors. The mammary gland was chosen as a model for the study of the role of β_1 integrins in branching morphogenesis, differentiation and involution. In transgenic mice expressing β_1 integrin lacking the extracellular domain, the development of the gland during pregnancy and lactation appeared to be delayed due to increased apoptosis and delayed proliferation. There were also morphological changes, along with reduced lactation efficiency, in which the MAPK and Stat signalling pathways appeared to play a role. Furthermore the role of EGF signalling and of FGF10 and the FGF-receptor 2b in branching morphogenesis were identified. These studies contributed important data to support the concept that adhesion systems, in cooperation with growth factor signalling, are crucial in controlling epithelial cell plasticity.

The epithelial-mesenchymal transition (EMT) during invasion and metastasis of epithelial malignancies was studied using the NBT-II rat bladder carcinoma cell model. These cells were found to undergo EMT when exposed to FGF-1, EGF or SF/HGF. EMT required activation of c-src and of the ras-MAPK pathway. As was initially shown by Tchao, also the contact with native collagens induced EMT. Thierry's lab showed that also laminin 5 can induce EMT. ***Slug*** *was identified as the transcription factor downstream of MAPK and responsible for the conversion of the epithelial in the fibroblastic phenotype.*

The experience gained with the NBT-II model is currently employed for the study of EMT during embryogenesis. In addition the NBT-II model is used to explore new concepts applicable to the progression of human tumours.

Have all these new activities affected your basic research?

I hope not, we will see. I need to keep a solid basic research program. If not we would dry out scientifically and I would die intellectually. And I have a good crew of promising young scientists in the lab that are actually doing the work.

Before we get up to make a little tour of the premises, Jean-Paul looks me in the eyes, with his characteristic boyish smile, and says 'You know, I have been a lucky guy. The way my career as a scientist has developed has been extraordinary. I do what I love to do and am good at and in a stimulating environment that allows me to realise some of my dreams. We all know that good fortune is not only a matter of chance. You have to put in a major effort to get somewhere and it is important to seize the opportunities as they present themselves. What's so special in my career is to have been able to work with exceptional very inspiring scientists.' He directs me to a corner in his office with a little stack of photo albums. We leaf through them and he gets excited at glancing over the pictures. 'Look here, this is me as a youngster at an EMBO meeting in 1971, together with all the big shots that made cell and molecular biology' (Fig. 1). And this one - with Jean Bernard, the great French haematologist - when I got the French Cancer League prize (Fig. 2). And this picture is priceless, with Günther Blobel and Gerald Edelman at the opening symposium of the new Curie Institute (Fig. 3). You know, to be in a picture with two Nobel laureates is one thing, but having been able to work with these guys has been very inspirational. Even though my professional life has much more administrative activities than I care for, I have remained close to the bench because of the opportunity to work with bright young scientists. Immensely stimulating and satisfying.

Jean Paul Thiery's contributions to biomedical sciences in 25 key papers

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