# *Preface*

Half a century ago, Rupert A. Willis (1) wrote *Embryologists and pathologists have much to gain by a better knowledge of each other's subjects*. Today, in the Molecular Era, we can ratify this idea and say that, in many ways, Oncology and Developmental Biology are two sides of the same coin (2). Cell migration and interactions with other cells and the extracellular matrix during embryonic development and tumor invasion are indeed a fine example of this. As a consequence, advances in our understanding of either of these areas will undoubtedly have a similar impact on both Embryology and Experimental Cancerology and even, on Therapy.

The importance of these links was always present in the mind of the Editors of this *Special Issue*. Experimental embryology was the start for one of us (MM), who later became a radiation oncologist with research activities centered on the molecular cell biology of cancer. As a medical student, MM worked under the supervision of Luc Vakaet (3), who brought the organ culture of cancer to the Laboratory of Prof. J. Fautrez in Ghent from his journey with Et. Wolff in France. In his cultures, Et. Wolff separated cancer cells from the normal embryonic tissue by a piece of vitelline membrane because he wanted to analyze soluble cancer growth factors (4). Vakaet and Mareel omitted the vitelline membrane and looked at invasion (5) in line with work done in other Laboratories (6,7,8,9). With a similar and mixed professional background as developmental biologist and surgical pathologist, the other Editor (J.A.) was trained as an experimental embryologist under the guidance of Miguel Guirao (Granada) and Francisco Orts-Llorca (Madrid), as molecular embryologist with Jean V. Ruch (Strasbourg) and Igor B. Dawid (Bethesda) and as experimental pathologist with Gunter F. Bahr (Washington, D.C.) and G. Barry Pierce (Denver). For all of these reasons, we thought that the current *Special Issue* would be timely since more and more emphasis is nowadays put on the similarities between invasion manifested by cancer cells and by normal embryonic and adult cells. We were honored that a number of experts in the fields of invasion and metastasis answered our invitation positively and sent most valuable paradigms. Other potential authors regrettably could not make it because of other commitments, so that our overview is admittedly incomplete.

The implication of oncogenes, tumor suppressor genes and their regulation was considered in much experimental detail by Garth Nicolson, interviewed here by Marc Mareel. From his biochemical background, Nicolson initiated the molecular analysis of metastasis. Most of the products of invasion and metastasis promoter and suppressor genes are regulated not only through gene mutation or LOH but also at multiple other levels. Amparo Cano found that the zinc finger transcription factor Snail downregulates E-cadherin (10). She and her coworkers review the mechanisms by which the expression of the E-cadherin gene is transcriptionally regulated both in development and in cancer. Riccardo Fodde's laboratory generated different mouse FAP models caused by hypomorphic *Apc* mutations (11). Together with Claudia Gaspar, he reviews here how different *Apc* mutations affect dosage of β-catenin explaining the role of the Wnt pathway in tumorigenesis.

Much of the work in the 1960-70's was merely descriptive. Later, however, experimental embryologists brought molecular insights into cancer and embryonic invasion. The interview of Masatochi Takeichi by Doug Sipp, telling how a developmental biologist found the first invasion suppressor molecule, provides a striking example of the relationship between embryonic development and cancer invasion. Malcolm Steinberg is known for his biophysical interpretation of cell seggregation on the

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**(1)** WILLIS, R.A. (1958) *The Borderland of Embryology and Pathology.* Butterworth and Co. Ltd., London. **(2)** See also: DAMJANOV, I. and MARTINEZ-HERNANDEZ , A. (1993) *Developmental Aspects of Neoplasia.* Int. J. Dev. Biol. Vol. 37, No. 1. **(3)** VAKAET, L. and MAREEL, M. (1964). Quelques précisions sur la régénération de l'endoblaste du blastoderme de poulet. *C.R. Soc. Biol.* 157: 902-903. **(4)** WOLFF, ET. and WOLFF, EM. (1959). Sur le comportement de souches cancéreuses humaines en association avec des organes embryonnaires de poulet cultivés in vitro. *C.R. Biol Biol* 2: 1898-1900. **(5)** VAKAET, L., VANDEKERCKHOVE, D. and MAREEL, M. (1971). Association de cellules HeLa avec de l'épithélium tubaire humain adulte. *C.R. Soc. Biol.* 165: 2225-2226. **(6)** ABERCROMBIE M. and AMBROSE E.J. (1958). Interference Microscope Studies of Cell Contacts in Tissue Culture. *Exp. Cell Res.* 15: 332-345. **(7)** LEIGHTON J.A. (1951). Sponge Matrix Method for Tissue Culture. Formation of Organized Aggregates of Cells in vitro. *J Natl Cancer Inst.* 12: 545-561. **(8)** EASTY G. and EASTY D. (1963). An organ culture system for the examination of tumor Invasion. *Nature* 199: 1104-1105. **(9)** SCHLEICH, A., FRICK, M. and MAYER, A. (1974). The Confrontation of Normal Tissue and Malignant Cells in vitro. Human Decidua Graviditatis and Hela Cells. A Model for Studies on Tumor Invasion. *Z. Krebsforsch.* 82: 247-255. **(10)** CANO, A., PÉREZ-MORENO, M.A., RODRIGO, I., LOCASCIO, A., BLANCO, M.J., DEL BARRIO, M.G., PORTILLO, F. and NIETO, M.A. (2000). The transcription factor Snail controls epithelial-mesenchymal transitions by repressing E-cadherin expression. *Nature Cell Biol.* 2: 76-83. **(11)** FODDE, R., EDELMANN, W., YANG, K., VAN LEEUWEN, C., CARLSON, C., RENAULT, B., BREUKEL, C., ALT, E., LIPKIN, M., MEERA KHAN, P. and KUCHERLAPATI, R. (1994). A targeted chain-termination mutation in the mouse Apc gene results in multiple intestinal tumors. *Proc. Natl. Acad. Sci. USA* 91: 8969-8973.

basis of differential cell-cell adhesion. His work covers this topic all the way from embryonic self-assembly to cadherins. Together with Ramsey A. Foty, he discusses how not only E-cadherin but also N-and P-cadherin influence cell segregation in embryonic development and cancer invasion. The role of matrix metalloproteinases (MMP) in multiple cellular activities during various steps of cancer progression are discussed by Carlos Lopez-Otin and coworkers. They provide putative explanations for treatment failures and propose new MMP inhibition strategies. Migration, the cytoskeleton and invasion were topics covered by the Microtubule Meetings organized by Marc De Brabander at Janssen Pharmaceutics in Beerse, Belgium. Juri Vasiliev was one of the participants. Three decades later, we are happy to receive from him a most remarkable and richly illustrated overview about the role of the cytoskeleton in the locomotion of epitheliocytes and fibroblasts in 2D cultures. Whereas most of the cell migration literature concentrates on single cells on solid substrates, Peter Friedl discusses the migration mechanisms of coherent groups of cells, which are probably more relevant for invasion than single cells. The work of Peter Friedl caught our attention because of the detailed morphological and molecular analysis of coordinated cell migration (12). From these and other reviews it becomes quite clear that invasion comprises a number of cellular activities the correct regulation of which is needed for embryonic development and for maintenance of structural and functional integrity of adult tissues: cell-cell adhesion; cell-matrix interaction; migration; proteolysis; ectopic death or survival. Together, the coordinated regulation of these activities establishes the invasive growth program, an idea launched by Paolo Comoglio's group (13). With Alessandra Gentile, he reviews the coordinating role of the hepatocyte growth factor (HGF) /c-Met receptor pathway in the cellular activities associated with invasion.

Remarkably, invasion and metastasis research has been furthered greatly by Doctors of Veterinary Medicine. One of them Josh Fidler, is interviewed here by another one Ian Hart, his former student. The influence of Josh Fidler's work on thinking about invasion and metastasis at both sides of the Ocean can hardly be overestimated. One exciting aspect of the participation of host cells in tumor invasion is that they may serve as targets for therapy. Marc Bracke and his coworkers recently turned their attention to N-cadherin, displaying both invasion-promoter and invasion-suppressor functions. Co-expression of several members of the cadherin family conveys one level of complexity for our understanding of the invasion-suppressor function of E-cadherin (14). Another level of complexity is the finding that one protein may contribute to opposite cellular activities depending upon the complex in which it is embedded. A striking example is β-catenin as described by Juergen Behrens. He performed the experiments that established the invasion-suppressor role of E-cadherin (15). This work also lead to the recognition of the role of other elements of the E-cadherin/catenin complex (16). In the latter complex β-catenin acts as an invasion-suppressor; in the Wnt pathway it acts as an oncogene as discussed here by Jürgen Behrens and Barbara Lustig. Defining the elements of epithelial tumor micro-environments, with particular emphasis on leukocytes and cytokines and manipulating this to therapeutic advantage are Frances Balkwill's goals (17). Here, she and her coworkers discuss how this large family of chemokines and their receptors can contribute to cancer spread.

Participation of the host in invasive processes has received growing attention. Didrik Laerum interviewed by Dieter Hülser, a cell biologist whom he met in Tübingen, worked in collaboration with Leo de Ridder. They developed a realistic substrate for brain tumor invasion, bringing embryonic brain cells into culture and let them differentiate before confrontation with the brain tumor cells. Normal cells participate also in cancer cell invasion. Indeed, tumor invasion and metastasis does not result solely from cancer cell activity but is largely governed by cross talk with the host, as described now more than a century ago (18). These host reactions are manifested by desmoplasia, angiogenesis and infiltration by immunocytes and inflammatory cells. Examples of host cells participating in cancer invasion, discussed here, are myofibroblasts and inflammatory leukocytes. Myofibroblasts are associated with the name of Giulio Gabbiani (19,20) and he and his coworkers discuss how the interaction of myofibroblasts with other cells controls fibrotic diseases and tumor progression. Two lines of research by Flemish workers drew attention to the dual role of leukocytes in tumor biology. One reported that non-metastatic tumor cells become metastatic when they fuse with activated lymphocytes (21). The other launched the intriguing concept of

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countercurrent invasion (22). Here, Ghislain Opdenakker and Jo Van Damme focus on the mechanisms by which chemokines may assist tumors to invade and metastasize and how this may influence the oncologist's thinking and acting.

Another example of the relationship between embryonic development and cancer invasion is illustrated by the carreer of Jean-Paul Thiery, interviewed about his insights into the molecular mechanisms of invasion, migration and the epithelial to mesenchymal transition by the pathologist Fred Bosman . Invasion is not unique to cancer cells. Germ cells are also relevant to the present *Special Issue* because they migrate over large distances in the embryo and because, at least in the chick, they represent the only embryonic invaders which metastasize via the circulation. Christopher Wylie, whom one of us (MM) met during the seventies in the Laborartory of Ruth Bellairs at University College London, has studied germ cell migration for several decades. He and Kathleen Molyneaux discuss how in three species, namely the mouse, *Drosophila* and Zebrafish, primary germ cell migration is initiated and how these cells find and arrest at their targets. Later on, Juan Aréchaga, Marc Mareel and coworkers write about the pathological "caricature" of germ cell migration, discusssing germinal tumor invasion.

Lance Liotta, a pathologist at the NIH, interviewed by his former student Vincent Castronovo, wanted to bring invasion research closer to the natural situation and pioneered *in vitro* and *in vivo* methods to reach his goal. We invited Adriana Albini and Gerhard Christofori to write review papers about curent trends in such methods. Whilst working in the Laboratory of George Martin and Hynda Kleinman, Adriana Albini developed a rapid, reproducible and highly relevant *in vitro* chemo-invasion assay (23) which became most widely used. She and her coworkers describe the assay, with emphasis on lytic enzymes and their inhibitors and they discuss major results obtained with the assay. Gerhard Christofori provided direct evidence for the role of cell-cell adhesion in invasion using a transgenic mouse model for β-cell tumors of the pancreas (24). With his co-worker Ivana Crnic he reviews recent developments in metastasis models, emphasizing the application of modern high throughput molecular technology to material directly taken from human cancers.

Finding new therapeutic strategies is a major goal of cancer research. Suzanne Eccles emphasizes the parallels between normal, developmental or angiogenic and cancer invasion. Her review explores these parallels and searches for pivotal points in cancer cell-host cross-talk as well as in pro-invasive signal transduction for therapeutic intervention. Successful cancer treatment using host cells as a target is illustrated by radiotherapy of bone metastasis. We asked two clinical radiotherapists at our Department, Luc Vakaet, Jr. and Tom Boterberg, who spent four years in the Laboratory of Experimental Cancerology(25,26), to review the clinical and molecular aspects of this treatment.

We sincerely hope you enjoy and benefit from this rich compendium of timely research papers, the publication of which has been made possible by the interest and generosity of its contributing authors and by the editorial excellence of the Editorial Team of *The International Journal of Developmental Biology*.

*Marc Mareel and Juan Aréchaga*

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