CANCER and COMMUNICATION

The bio-communicative processing strategies of tumor(cell)s

Int. Congress, 2 – 5 July 2009 Salzburg - Austria

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Programme

and

Book of Abstracts

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Welcome!

We wish you a beautiful
and
interesting stay in Salzburg

Salzburg
(Austria)

2 - 5 July 2009

Programme
and
Abstracts

of
Talks

organized by

Erich Hamberger and Günther Witzany

in co-operation with

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Programme

St. Virgil Conference Center
Ernst-Grein-Straße 14, A-5026 Salzburg, Austria
Tel.: +43/662/65901-0 | Fax: +43/662/65901-509
E-Mail: office@virgil.at

Wednesday, July 1st, 2009

12:00 – 20:00	Registration at St.Virgil
18:45	Welcome drink and warm reception by the cooperating partner Alfred Winter (Government of Land Salzburg) and Peter Eckl (Department of Cell Biology. University of Salzburg)

Thursday, 2nd of July 2009

Morning Chair: Witzany
9:00 – 12:30

09:00 - 09:15
Erich Hamberger:
Motives to organize this congress

Opening talk
Harald ZUR HAUSEN:
Viruses causing cancer

Tadatsugu TANIGUCUI:
Nucleic Acids, Interferons and Immunity: Implications in Cancer Therapy

11:00 – 11:30 **Coffee Breack -Tea Time**

Yuri LAZEBNIK
On the consequences of cell promiscuity, or whether viruses can cause cancer by fusing cells

Afternoon: Chair: Hamberger
14.30 – 17.30

Günther WITZANY
Biocommunication of Cancer Cells from the „Virus first"-Perspective

Guiseppe CARRUBA
Steroid Enzymes and Cancer

16:00 – 16:30 **Coffee Breack -Tea Time**

Martin LACKMANN
/Eph on – Eph off: /insights into molecular switches that (mis)guide cancer cell positioning

Open discussion

Friday, 3rd of July 2009

Morning: Chair: Hamberger
09:00 – 12:00

Leon BIGNOLD
Morphology of tumours and cell-cell communication

James E. TROSKO
Cancer as a Stem Cell Disease, a Disease of differentiation, and a Disease of Homeostasis: The role of Cell–Cell Communication

10:45 – 11:15 **Coffee Breack -Tea Time**

Erna PAP
Letter in an envelope - microvesicular information transfer. A new way of cell-to-cell communication

Afternoon: Chair: Witzany

14.00-17.00

Ulrike KÄMMERER
The human placenta as a „well behaving tumour" and model to study regulation of cell growth, proliferation and invasion

Mariano BIZZARRI
Complexity and Cancer: self-organizing attractors and non-linear dynamics of regulatory networks

15:45 – 16:15 **Coffee Breack - Tea Time**

Marty SERENO
Cells, Language and Communication

Open discussion

Evening:

18:45 – 21:00 (6.45 p.m. - 9.p.m.)
Invitation to the Congress-dinner by the local organizer committee in St. Virgil
"Everyone is welcome"

19.00 – 19:30 (7. p.m. - 7.30 p.m.)
Cultural performance (Bernadette Furch, Alt; Hassan Mahmoud, Oud)

Saturday, 4th of July 2009

Morning: Chair: Witzany
09:00 – 12:30

Manuela BACCARINI
Targets of the Raf pathway in tumorigenesis

Karin de VISSER
The inflammatory tumor microenvironment: Tumor-protective or Tumor-promoting?

10:30 – 11:00 **Coffee Breack -Tea Time**

Angelika RIEMER
Interactions between the Immune System and Cancer / Immunotherapy Approaches

Veronika SEXL
Tumor surveillance in leukemia

Afternoon: Chair: Hamberger
14:30 – 17:30

Mary Helen BARCELLOS-HOFF
Rethinking Radiation Carcinogenesis

Ana SOTO
The Tissue Organization Field Theory

15:45 – 16:15 **Coffee Breack -Tea Time**

Erich HAMBERGER
Cancer and Message Transduction. Fragments of a Bio-Communication-Approach for a better Understanding of Carcinogenesis

General open discussion / Closing remarks

Speakers / Titles of the Talks

Manuela **BACCARINI**, Vienna (Austria): *Targets of the Raf pathway in tumorigenesis*

Mary Helen **BARCELLOS-HOFF**, New York (USA): *Rethinking Radiation Carcinogenesis*

Leon **BIGNOLD**, Adelaide (Australia): *Morphology of tumours and cell-cell communication*

Mariano **BIZZARRI**, Rome (Italy): *Complexity and Cancer: self-organizing attractors and non-linear dynamics of regulatory networks*

Guiseppe **CARRUBA**, Palermo/Sicily (Italy): *Steroid Enzymes and Cancer*

Erich **HAMBERGER**, Salzburg (Austria): *Cancer and Message Transduction. Fragments of a Bio-Communication-Approach for a better Understanding of Carcinogenesis*

Harald zur **HAUSEN**, Heidelberg (Germany): *Viruses causing cancer*

Ulrike **KÄMMERER**, Würzburg (Germany): *The human placenta as a „well behaving tumour" and model to study regulation of cell growth, proliferation and invasion*

Martin **LACKMANN**, Victoria (Australia): */Eph on -- Eph off: /insights into molecular switches that (mis) guide cancer cell positioning*

Yuri **LAZEBNIK**, New York (USA): *On the consequences of cell promiscuity, or whether viruses can cause cancer by fusing cells*

Erna **PAP**, Budapest (Hungary): *Letter in an envelope - microvesicular information transfer. A new way of cell-to-cell communication*

Angelika **RIEMER**, Boston (USA)/Vienna (Austria): *Interactions between the Immune System and Cancer / Immunotherapy Approaches*

Marty **SERENO**, London (UK): *Cells, Language and Communication*

Veronika **SEXL**, Vienna (Austria): *Tumor surveillance in leukemia*

Ana **SOTO**, Boston (USA): *The Tissue Organization Field Theory*

Tadatsugu **TANIGUCHI**, Tokyo (Japan): *Nucleic Acids, Interferons and Immunity: Implications in Cancer Therapy*

James E. **TROSKO**, Michigan (USA): *Cancer as a Stem Cell Disease, a Disease of differentiation, and a Disease of Homeostasis: The role of Cell–Cell Communication.*

Karin de **VISSER**, Amsterdam (NL): *The inflammatory tumor microenvironment: Tumor-protective or Tumor-promoting?*

Günther **WITZANY**, Bürmoos/Salzburg (Austria): *Biocommunication of Cancer Cells from the "Virus first"-Perspective*

ABSTRACTS
Of
Talks

CANCER and COMMUNICATION
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Targets of the Raf pathway in tumorigenesis.

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Ras and Raf were among the first oncogenes discovered. Their role in cellular transformation is well documented in the literature, and activating mutations in Ras or in B-Raf are frequently found in human tumours. As a result, the ERK pathway is activated in the majority of human tumors. The aim of our project is to identify the molecular mechanism(s) underlying the unique functions of Raf family members Raf-1 and B-Raf and to explore their connection to tumorigenesis. To this end, we are using mouse strains in which Raf-1 and B-Raf can be conditionally ablated by the *Cre/loxP* system to investigate the role of the Raf kinases in tumor development and maintenance and in metastasis. In particular, we have been studying the role of Raf-1 in skin tumorigenesis. We find that Raf-1 plays an essential role in the development and maintenance of Ras-induced epithelial tumors. The role of Raf-1 in skin tumorigenesis is to prevent differentiation, likely by restraining the activity of its associated kinase Rok-alpha, which is hyperactive in Raf-1 knock-out keratinocytes. We have also identified the structural requirements for the interaction between Raf-1 and Rok-alpha, which should serve as a basis for the design of inhibitors of this interaction.

Keywords: Raf kinases, Ras-driven tumorigenesis, skin, protein-protein interaction

Rethinking Radiation Carcinogenesis

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Ionizing radiation is one of a few well-documented carcinogens in humans and experimental animals. Mechanistic understanding of how the biological processes elicited by radiation can increase cancer risk is important for evaluating risk from different exposures and as a prototype to understand the potential of other environmental exposures. Many attribute radiation's carcinogenic potential to well-documented targeted effects from the interaction of energy and DNA that may result in mutations. It is becoming increasingly recognized that radiation can also alter signaling, phenotype and multicellular interactions by poorly understood non-targeted effects. Targeted effects that alter genomic sequence are proportional to dose while non-targeted effects that alter gene expression, cell signaling, genomic stability and cell phenotypes are generally not proportional to dose, and thus have not been incorporated into the radiation carcinogenesis paradigm. Our experimental data and that of others suggest that radiation carcinogenesis is really a two-compartment problem. Using a novel mouse mammary chimera model, we show that host response to low doses of sparsely ionizing radiation promotes epithelial cancer in unirradiated tissue. Understanding of targeted and non-targeted radiation effects underscore the concept of cancer as an emergent phenomenon resulting from altered tissue interactions and signaling, rather than from cellular defects.

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orphology of tumours and cell-cell communication

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Tumour cells primarily exhibit excess growth, but also show many additional histologic abnormalities/traits including nuclear 'atypia', loss of specialization and invasiveness. However, the phenomenology of these traits is complex.
First of all, tumours occur as separate, identifiable types, which can be considered as non-random combinations of such traits. Among all the tumour types, the various traits including nuclear 'atypia', loss of specialization and invasiveness occur independently. (1)
Another complex aspect of tumour cell traits is that their particular combinations often relate to the cell type of origin. Thus while the combination of traits for 'basal cell carcinoma' arises in the epidermis, there is no recorded example of a 'basal cell carcinoma' arising in the small intestine. Similarly, 'benign giant cell tumours' of fibrocytes occur, but not 'benign giant cell tumours' of chondrocytes or adipocytes. An addition aspect of this 'cell-of-origin-specificity' of tumour types/trait combinations is that hereditary predispositions are in most cases to specific tumour types arising in specific cell types. Thus in familial polyposis, the predisposition is to colonic adenomas, but in hereditary non-polyposis colo-rectal cancer, the predisposition is to carcinomas without pre-existing adenomas.

The fundamental question which these phenomena raise is: when the genome of all cells in the one individual is the same, why do only some tumour types (i. e. some combinations of traits) arise in only some cell types? (2, 3).

Finally, two features of tumours indicating cell-cell communication are discussed. The first is the occasional reactions of stromal cells to the presence of carcinomas. The main example is 'desmoplasia' (seen especially in scirrhous carcinoma of the breast) in which fibroblasts adjacent to carcinoma cells show excess production of collagen. Another example is 'osteosclerotic' reactions to carcinoma cells of certain types metastatic in bone.
The second feature is 'adjacent atypia', which can be divided into (i) a kind characterized by 'continuous radiating and diminishing' atypia, seen for example in breast carcinomas, and (ii) a kind characterized by 'new foci adjacent but with intervening normality', seen for example in superficial multicentric basal cell carcinomas of the skin.
Possible explanations of these phenomena will be discussed.

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Complexity and Cancer: self-organizing attractors and non-linear dynamics of regulatory networks

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Until now cancer has been recognized has a cell disease, mainly due to altered-mutated gene expression, leading to several phenotype and metabolic modifications explained on a basis of a oversimplified cause and effect relationship, generally described by linear mathematics. However, it is increasingly clear that living cells are complex systems, evolving according to a non-linear dynamics of gene-regulatory networks. A cell population, during its life, travels along several “state-spaces” (attractors), that manifest the global dynamics of the systems; each state in the phase-space can de described by an integrated set of genetic, metabolomic or epigenetic parameters, now available by means of high throughputs techniques; monitoring the evolution and behavior of cancer cell population by means of fractal dimension could provide a reliable and useful quantitative morphological parameter of complexity, suitable to properly define the space-state. Life is a far-from equilibrium process which maintains its local level of organization at the expense of the larger global entropy budget. According to the thermodynamics of non-equilibrium, attractors are generally working at “the edge of chaos”, a characteristic feature of dissipative systems that give rise to the emergence of more complex structures. In these conditions, the systems is highly sensitive even to small pathogenic perturbations related to both genetic and non-genetic influences (disruption of cell-stroma signalling, extracellular matrix remodelling, shape distortion, modification in the tissue architecture), and it is though to evolve into abnormal, unexpected basin of attraction, characterized by change in complexity rate and reduced stability. A compelling set of data suggests that cancer cells are trapped into “embryonic-like attractors”, switching to an embryonic-fetal metabolism and displaying a marked sensitivity to morphogens and regulatory signals of both maternal and embryonic origins. This framework considers that biological information cannot be solely reduced to digital-DNA- encoded data, but instead should include driving forces embedded in the “epigenetic landscape”; moreover, in depicting trajectories performed by cancer cells through different attractors in the phase-space, it could help in identifying the effective Achille’s heal of the disease.

Steroid Enzymes And Cancer

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Sex hormones act as intermediaries between exogenous (environmental, dietary) factors and molecular targets in development and progression of hormone-related tumors, including classical breast and prostate, and nonclassical colorectal and liver carcinomas. Breast and prostate cancer represent the most common non-skin neoplasms respectively in women and men of western countries. Although they are widely recognized as prototypes of age-related, hormone-dependent tumors, many epidemiologic studies have investigated the association between circulating sex steroids and breast or prostate cancer, but the resulting data have been largely inconsistent and inconclusive. Paradoxically, in fact, both total and bioavailable serum estrogen (estradiol) or androgen (testosterone) significantly decline with age, eventually leading to an inverse relationship between circulating hormones and the risk of developing breast or prostate cancer, respectively. Although several issues related to measurement of plasma steroids, both androgens and estrogens, could be considered to explain this large inconsistency of data, it is highly unlikely that a single assay of circulating steroid hormones can be considered representative of their average levels over an etiologically relevant time of life. In this respect, it ought to be emphasized that the time scale of either breast or prostate carcinogenesis and tumor progression can span 35-40 years or longer. Therefore, the timing for the carcinogenetic impact of androgen and/or estrogen on human breast or prostate should be allocated 20-30 years (or even earlier) prior to the clinical manifestation of the tumor, when serum levels of bioactive hormones are higher and yet potentially relevant. In any case, a critical issue remains to what extent circulating hormones can be considered representative of their intratissue levels. Levels of sex steroids in peripheral target tissues, including breast and prostate, have been reported to be strikingly greater (10 to 100-fold) than the respective plasma values. Nontumoral and malignant breast or prostate tissues and cells are equipped with enzymes of steroid metabolism, including 17□hydroxysteroid dehydrogenase (17□HSD), 5□-reductase, 3□/3□HSD, hydroxylases, sulfatases, sulfotransferases, and aromatase. A divergent expression and/or activity of these enzymes may eventually lead to a differential accumulation of steroid derivatives having distinct biological activities in target tissues, with profiles of intratissue steroids that may substantially diverge from their plasmatic counterpart. In this respect, it has been proposed that circulating hormones are not the drivers of estrogen or androgen action at peripheral level, but they instead represent a reflection of steroid uptake and biotransformation at extragonadal sites, including breast and prostate: in other words, they are reactive rather than proactive. Based on data from our own studies, three pointed examples are presented to corroborate the above inferences.

Firstly, the assessment of intratissue levels of estrogens in both nontumoral and malignant human breast indicated that hydroxy-estrogens account for over 80% of all tissue estrogens and that significantly greater amounts of both 2- and 4-hydroxyestradiol, along with a marked increase of 16a-hydroxyestrone, are observed in cancer with respect to *normal* breast tissues.
In second place, locally produced or metabolically transformed estrogens may differently affect proliferative activity of prostate cancer cells, with estrogen either stimulating or decreasing prostate tumor cell growth, also depending on the balance between wild-type and variant estrogen receptor (ER) a and ERb.
Lastly, both expression and activity of the aromatase enzyme, that converts androgens into estrogens, are elevated during liver carcinogenesis and tumor progression, being associated with an imbalance of wild-type ERa and its variants ER46 and ER36, and with the expression of amphiregulin, a member of the family of EGFR ligands.
This combined evit target tissue level, as governed by local concentration and activity of steroid enzymes, is a dence strongly supports the conception that the metabolic fate of circulating steroids adecisive issue to determine the ultimate biomolecular impact of sex hormones in either nontumoral and malignant steroid target tissues, including breast, prostate and liver.

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Cancer and Message Transduction. Fragments of a New Bio-Communication-Approach for a Better Understanding of Carcinogenesis.

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With the biological revolution in the second half of the twentieth century also cancer research totally reshaped. Now, about half a century after the discovery of the DNA double helix and the victory-run of molecular biology, we have an abundance of information about the molecular and cellular mechanisms in cancer.
But do we have also a clearer understanding concerning the “complex communicative acting”, the processing strategies of cancer cells, cancer organs, while we know a lot of singular signalling pathways on the molecular level of human cells?
Following the hint of Trosko, that “the more fundamental change in cancer research [as on the technical level] will be conceptual” (Trosko 2004) in the contribution should be presented a Bio-Communication-Approach, based on the idea, that living entities – and cancer as well as a special form of living entity – cannot be fully accounted in terms of the principles and laws of physics and chemistry alone (Ji 1999). They require in addition a vocabulary, that is able to point out living entities as “communicative agents” with the ability to sign-mediated and word-analogous interaction/bio-communication.
In this context the expression “message transduction” should be established in bio-sciences with help from Capurro *(Theory of Message, 2003).*
Based on Barbara Mc Clintock's consideration in her Nobel lecture in 1983, that a goal for the future in biological science would be to determine the extent of knowledge a cell has of itself and how it utilizes this knowledge when challenged (Mc Clintock 1984) should be discussed finally with help of the rediscovered Austrian language philosopher Ferdinand Ebner, in which way(s) the visionary thought of McClintock can be adapted in actual cancer research; that means to confront us with the question what kind of knowledge and communicative competence cancer cells (organs) have of themselves and how they utilize this competence within the process of carcinogenesis.

Keywords: Message transduction, bio-communication, cancer theory

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Viruses causing cancer

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No abstract received.

The human placenta as a „well behaving tumour“ and model to study regulation of cell growth, proliferation and invasion.

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A successful human pregnancy depends on proper formation of the hemochorial placenta. In order to attach the placenta to the wall of the uterus, anchoring villi are developed which are composed predominantly of trophoblast cells. Those trophoblast cells originate from the “trophoblast layer” which forms the outer surface of the implanting blastocyst, the very early embryo. Further, to nourish the developing embryo (and later the fetus), the human placenta is characterized by an extensive infiltration of the maternal tissue and especially the uterine vessels by extravillous cytotrophoblast cells (EVT), a subpopulation of trophoblast cells which evade from the top of the anchoring villi. EVT represent epithelial cells with fascinating properties: They are able to fuse to form syncytia, can behave like immotile but proliferating epithelial cells or undergo a mesenchymal-like transformation that converts them into non proliferative and highly invasive cells. Thus, the biological behaviour of EVT resembles parallels with the processes of invasion and metastasis seen in malignant tumours. Concerning the tumour like attributes of EVT, those cells do express and activate enzymes (e.g. Metalloproteinases) enabling them to degrade the extracellular matrix and they secrete chemokines (Il-8, CCL2) and cytokines (e.g. IL-10, TGF-beta) which manipulate the maternal immune system in order to accept the invading foreign fetal EVT in a mechanism similar to the immune escape of tumour cells. The downregulation of classical MHC molecules – which is also typical for tumour cells - associated with the expression of unusual MHC molecules like HLA-G and -E further enables the placenta to inhibit the attack aggressive immune cells. Concerning metabolism, the placenta has to function and survive in a hypoxic environment. Like tumour cells, the EVT are able to increase their aerobic glycolysis and produce lactate. The latter further can be seen not only as a by-product of metabolism but rather as a substance that helps the EVT and tumour cells as well to boost invasiveness in an autocrine matter, to silence potentially harmful immune cells and to destroy the stroma cells in the tumour-stroma like placental bed. However, unlike cancer cells, in case of placentation these attributes of EVT are only transient in nature, with defined temporal and spatial margins reflecting that their proliferation, migration, and invasiveness in situ are stringently controlled. Therefore, the human placenta could be seen as a 'well-behaving' tumour.

This talk will give an overview on the “tumour like” features of the placenta, introduce parallels of EVT and tumour cells which make the placentation an outstanding physiological model for identifying mechanisms underlying epithelial tumour progression and interaction and communication with the “host”. Finally, the differences which in the end distinguish the benign tumour placenta from malign tumours and what we can learn from them how invasive growth could be controlled.

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"Eph on -- Eph off: insights into molecular switches that (mis) guide cancer cell positioning."

Martin Lackmann

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Eph receptor tyrosine kinases (RTKs) together with membrane-bound ephrin ligands act as developmental cell guidance cues which control motile cell behavior and relay spatial information by modulating cell-cell adhesion and detachment[1]. Developmentally-regulated Eph/ephrin signaling underlies the patterning of nervous, vascular and skeletal systems, while the unscheduled, de-regulated function of these cell surface proteins is involved in disease progression of invasive and metastatic cancers[2].
Eph-guided cell positioning relies on receptor expressing cells translating ephrin abundance on interacting cells into precisely-modulated cellular responses. In the context of cancer pathology, considerable evidence suggests that depending on the type and stage of disease, Eph/ephrin interactions can promote or prevent tumour growth, invasion and metastasis[3]. Thus, in colon cancer EphB2 and EphB3 act as tumour suppressors[4], while large-scale array analyses of cancer patient samples for somatic mutations singled out EphA3 as one of the most prominent candidate cancer genes in colon[5] and lung cancer[6], melanoma and glioblastoma[7]. Of note, Eph receptors, in contrast to other RTKs, elicit cellular responses even when mutations prevent kinase activation, so that interaction with ephrins results in tight cell-cell adhesion: Effectively, the capacity to support or suppress Eph kinase signaling dictates if cells respond to ephrin contact by detachment and segregation or by adhesion and invasion, respectively[1].
We have used a range of biochemical, cell-biological and single-cell imaging strategies to unravel molecular concepts underlying this Eph/ephrin-based cell-cell communication. We find that EphA3-mediated cell-cell repulsion requires the active kinase to promote:
- cytosolic signalling cascades that trigger cytoskeletal contraction and cell rounding
- functional association with the Eph receptor of the ADAM10 metalloprotease, which cleaves Eph-bound cell-surface ephrin and disrupts the molecular seam tethering the interacting cells[8, 9]. Eph RTK activity in turn is controlled by corresponding tyrosine phosphatases, which not only regulate downstream signalling and cellular responses, but also are part of the molecular switch that allows cell-cell segregation to occur. Interestingly, in a range of solid tumours EphA3 is abundantly expressed in the stromal and vascular compartment, and modulation of its kinase activity with an agonistic monoclonal antibody has pronounced effects on tumour progression.

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On the consequences of cell promiscuity, or whether viruses can cause cancer by fusing cells.

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The ability to fuse cells is shared by many viruses, including common human pathogens and endogenous viruses. We proposed that cell fusion can link viruses to carcinogenesis and tumor progression by causing chromosomal instability and by combining properties of distinct cells. I will overview the data underlying this hypothesis, discuss its implications, and present our results.

Letter in an envelope - microvesicular information transfer. A new way of cell-to-cell communication.

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Microvesicles (MVs) are membrane-covered small particles, shedding from various cell types. It is a relatively recent finding that MVs represent a pivotal role in information transfer between cells, as cellular effectors. Their recognition has opened a new era in the understanding of cellular communication, not only in the vicinity, but in far distances as well.

The nomenclature is still controversial: exosomes, microvesicles, microparticles, ectosomes and even apoptotic bodies are commonly used terms. In the present talk we use the collective term „microvesicle" for all subcellular vesicles ranging from 30 to 1000nm.

MVs have been identified to originate from a large number of cell types *in vivo* and *in vitro*: among others from epithelial, fibroblast, haematopoetic, immune, trophoblast and tumor cells. Besides a constitutive release, the secretion of MVs is enhanced upon cell activation or apoptosis. MVs display a variable spectrum of molecules, enclosed inside the vesicles and inserted in their membrane, a pattern specific for the donor cell that secretes them. Therefore on the one hand „packages" of informations can reach different targets, allowing a special communication between cells, on the other hand, the newly arriving molecules can modify the protein (lipid, nucleic acid) set of the acceptor cells, providing new phenotype to them. MVs play a role in several physiological and pathological processes, such as immune modulation in inflammation and during pregnancy, blood coagulation and cancer.

MVs released by tumor cells could be detected in plasma, sera and other body fluids, also *in vitro* in cell culture supernatants. Although different characteristics of these MVs have been reported, all reflect the special potential of tumor cells for survival and the expansion of the tumor. They promote angiogenesis, chemoresistence, they carry FasL inducing apoptosis of cytotoxic lymphocytes, furthermore they can mediate the „horizontal propagation" of oncogenes.

The present talk aims to highlight some aspects of this newly recognized way of cellular communication: the „microvesicular network", and its implication in cancer. MVs may serve not only as prognostic markers in different diseases, but could also hold the potential to be new therapeutic targets or drug delivery systems. This allows a new approach in the understanding of the nature of tumors, therefore new possibilities can be addressed for cancer therapy .

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Interactions between the Immune System and Cancer / Immunotherapy Approaches

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Interactions between the immune system and tumors are complex. On the one hand, chronic inflammation can promote tumorigenesis. On the other hand, the immune system can destroy transformed or malignant cells, a process known as immune surveillance. However, immune surveillance is not always successful, resulting in 'edited' tumors that have escaped the surveillance mechanisms. Tumors that arise despite immune surveillance have been sculpted by the immune system, often resulting in the outgrowth of cells that are less immunogenic. Established tumors additionally tend to generate immunosuppressive microenvironments that can block productive antitumor immunity. As these manifold interactions between tumors and the immune system have only been investigated in recent years, early immunotherapy approaches – both monoclonal antibody and cellular therapies – have not rendered major therapeutic breakthroughs. Through a deeper understanding of the complicated relationship between tumors and the immune system, tumor immunology today strives to harness the immune system to generate protective antitumor responses in patients. The most famous success story of immunotherapy in recent years is the passive application of the anti-HER-2 monoclonal antibody trastuzumab in a subset of breast cancer patients. Our own research has focused on replacing this passive infusion of antibodies by an active vaccination with epitope mimics, so-called mimotopes, resulting in antibodies of the same specificity. Another hot topic in immunotherapy are HPV-induced cancers. Two prophylactic vaccines are currently available, but no therapeutic immune intervention for people who are already infected with this virus. HPV-induced lesions are a classic example of (pre)cancers susceptible to T cell immunity. On the other hand, HPV has developed numerous immune evasion mechanisms, ranging from simple hiding to active suppression of communication between infected and host immune cells. Considering these aspects, my current research interest lies in designing a broadly applicable T cell vaccine against HPV-induced cancers.

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Cells, Language, and Communication

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Many comparisons have been made between cellular coding systems and human language. Despite recent attempts to make this analogy more productive, it has maintained its reputation as a plaything for retired scientists. I think there are actually very deep, exciting, and fruitful conceptual similarities between these two very different systems. More precisely, there are exactly two naturally-occurring examples (and as yet, no artificial example) of this particular kind of symbol-using representational system on the Earth. The first, single-celled version of such a system arose from a chemical prebiotic substrate at the origin of life, initiating Darwinian evolution. Subsequently, multi-cellular organisms evolved and they developed elaborate humoral and neural control mechanisms; but a similar, autonomous symbol-using system did not reemerge on any intermediate level until the origin of thought and language from the substrate of prelinguistic neural activity patterns in the brains of early hominids. Understanding the relation between these two unique code-using systems has been impeded because of a difficult starting point for the analogy. Despite many crucial similarities in the architecture of code use, the two systems differ in a key way because code is not directly used for communication in one of them.
Though a large part of my work has tried to draw upon the structure and function of the cellular system to make predictions about the substrate for human language comprehension, the analogy also throws a new light on the nature of cellular code use and communication.

Tumor surveillance in leukemia

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Transformed cells need to escape the immunological control in order to spread in the organism. We have shown in the past that NK cells are key components for the control of bcr/abl transformed leukemic cells. We have defined Stat1 and PI3K as important regulators of this interaction.
We were also interested to understand whether common additional mutations occurring in tumor cells alter the responsiveness of leukemic cells to the immune system. To study this we used a mouse model system for myc induced tumors. In order for a tumor to evolve a so called 2nd hit that complements myc induced tumorigenesis needs to occur. Tumor cells either disrupt p53 dependent signalling or up-regulate the anti-apoptotic protein bcl2.We found significant differences in the immunological control dependend on the nature of the 2nd hit. These data will be presented.

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The Tissue Organization Field Theory

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At the beginning of the 21st century, we are experiencing a paradigm change in biology. The realization that reductionism has failed to bring about an understanding of complex phenomena has resulted in reappraisals of old research concepts in embryology and cancer research. The dominant view during the last fifty years has been that development is the unfolding of a genetic program. This view guided the construction of developmental genetics, which according to Scott Gilbert is "a discipline that explicitly treated phenotype as a direct 'readout' of the nuclear genome". This perception is now being challenged by two disciplines, ecological developmental biology and developmental systems theory, both displacing the gene at the privileged causal agents.

Similarly, the dominant view of carcinogenesis, the *somatic mutation theory* (SMT) is both gene-centered and reductionist. The SMT views cancer as a cell-based disease. The premises of this theory are: 1) cancer is derived from a single somatic cell that has accumulated multiple DNA mutations, 2) cancer is a disease of cell proliferation caused by mutations in genes that control proliferation and the cell cycle, and 3) the default state of cell proliferation in metazoa is *quiescence*. The research program of the SMT adopted cell lines growing in 2-D cultures as the subject of research, thus reducing cancer to a cellular phenomenon. Additionally, neoplasms, which are 3D structures, were reduced to "transformed" cells. Because many facts challenge the predictions of this theory, a series of *ad hoc* explanations were offered resulting in a field rife with contradictions. Probably due to these shortcomings, an older tradition in cancer research centered at the tissue level of organization has been updated as the *tissue organization field theory of carcinogenesis* and is gaining momentum. This tradition originated in the late nineteenth century when pathologists began describing the histological pattern of tumors using the light microscope and suggested that altered tissue organization was at the core of neoplasia, thus linking carcinogenesis to embryonic development. In contrast with the *somatic mutation theory,* the *tissue organization field theory* (TOFT) postulates that: 1) carcinogenesis represents a problem of tissue organization, and 2) *proliferation* is the default state of all cells. A central motif in this theory is the persistence of morphogenic fields throughout adult life; these fields orchestrate histogenesis and organogenesis before birth as well as tissue maintenance and regeneration throughout postnatal life. The *tissue organization field theory* posits that neoplasms result from a flawed interaction among cells and tissues and that carcinogenesis is potentially reversible. Carcinogens, as well as teratogens, would disrupt the normal dynamic interaction of neighboring cells and tissues. Accordingly, understanding carcinogenesis will then require the use of animal models and/or 3D cultures where cells can organize into tissues resembling the topology and cellular diversity of observed in neoplasias *in vivo*. Experimentally, we are now engaged in an effort to first collect and then integrate data using a 3D tissue culture approach to finally unravel the mechanism of carcinogenesis. Present and future efforts in this direction will be presented and discussed.

Nucleic Acids, Interferons and Immunity: Implications in Cancer Therapy

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Host defense consists of two main aspects, namely, immune response to invading pathogens and suppression of tumor development. Our research in Immunology has stemmed from the original identification of two cytokine genes, namely, the genes encoding a type I interferon (IFN-□) and interleukin-2 (IL-2). In the context of the regulation of type I IFN genes, we identified a family of transcription factors, interferon regulatory factors (IRFs), which has recently gained much attention in terms of its critical role in linking the regulation of immune responses and oncogenesis. I will present our recent development of a new form of IFN-□, which may be useful for the treatment of viral and autoimmune diseases and cancer. I will then summarize the current status of the versatile functions of the IRF family members in the regulation of immune responses and other biological system with some evolutional consideration on this family. During microbial infection or tissue damage, DNA and RNA potently activate the innate and subsequent immune responses. I will summarize the current status on the deliberate divergence of the nucleic acid-mediated signaling pathways for the full-blown activation of innate immune responses, which may have implications in cancer therapy.
(Our work on IFN-□ is partly a long-lasting collaboration with Toray, Inc.)
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Cancer as a Stem Cell Disease, a Disease of differentiation, and a Disease of Homeostasis: The role of Cell –Cell Communication.

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From the single fertilized egg to the adult human being, consisting of ~100 trillion cells, composed of over 200 cell types, and classified into stem cells, progenitor or transit amplifying cells and terminally-differentiated cells, a delicate homeostatic regulation of cell proliferation, differentiation, apoptosis, adaptive responses of differentiated cells and senescence takes place by three communication processes [Extra-, Intra-, and gap junctional inter-cellular communication]. Gap junctional intercellular communication (GJIC) was first shown by W. Loewenstein to be responsible for growth control and normal differentiation. Later, the phenotypes of the loss of growth control or "contact inhibition" and of terminal differentiation were shown to be characteristics of cancer cells. Furthermore, when epigenetic chemicals, known to be teratogens or tumor promoters by their ability to induce oxidative stress-induced intra-cellular signaling, were shown to reversibly inhibit GJIC, and when anti-tumor promoters or cancer chemopreventive and chemotherapeutic agents were shown to either prevent the down regulation of GJIC by tumor promoters or to restore GJIC in non-GJIC tumor cells, additional evidence that GJIC played a critical role in the carcinogenic process. In addition, when various oncogenes and tumor suppressor genes modulated GJIC, a mechanistic basis for integrating exogenous factors (chemicals) and endogenous factors (oncogene and tumor suppressor gene proteins) was possible. The ability to isolate human embryonic/adult stem cells demonstrated that the maintenance of the non-differentiated state of these stem cells seemed to be the result of having non-functional GJIC. Upon induction of GJIC in stem cells resulted in the production of life-span limited progenitor cells that could terminally differentiate, senesce or apoptose. The demonstration that these adult stem cells could be "initiated" (to maintain their "immortalized" state) to start the carcinogenic process and ultimately become either "cancer stem cells" (identified by maintaining most of the phenotypic state of the normal adult stem cells) or "cancer non-stem cells"(being "partially-differentiated"). In summary, the concepts of cancer, described by C. Markert, B. Pierce, V.R. Potter, P.J. Fialkow, P.C. Nowell, & W.R. Loewenstein now seem to be supported by current understanding of the roles of stem cells and cell-cell communication in growth control, differentiation and apoptosis. The disruption of cell-cell communication leads to loss of growth control, of differentiation , of senescence and apoptosis, which characterizes cancer as a "disease of stem cells", a "disease of differentiation" and a "disease of homeostasis".

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The inflammatory tumor microenvironment: Tumor-protective or tumor-promoting?

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It is well established that communication between cancer cells and normal, healthy cells present in the tumor microenvironment is important for tumor outgrowth. Immune cells are one of the most abundant cell types found in the microenvironment of many tumors. The interplay between the immune system and cancer is rather controversial; both tumor-protective and tumor-promoting properties have been described. A deeper understanding of the temporal and spatial mechanisms regulating the inflammatory response and downstream pathways by which the immune system modulates sporadic cancer growth is critical for development of novel combinatorial therapies that target both cancer cells and tumor-supportive host responses. The overall goal of our research is to address the role and underlying pathways of the inflammatory tumor microenvironment during breast cancer progression and metastasis formation. We utilize a mouse tumor model that faithfully recapitulates human invasive and metastatic lobular carcinoma, e.g. a conditional mouse breast cancer model based on mammary epithelium-specific deletion of p53 and E-cadherin. Mammary carcinomas arising in this mouse model are characterized by abundant presence of innate immune cells, including degranulating mast cells and macrophages, T and B lymphocytes, antibody depositions and increased levels of pro-inflammatory mediators. Suppression of chronic inflammation attenuates premalignant progression and tumor formation. Preliminary data suggest a critical role of adaptive immune cells in outgrowth of metastases. By genetic elimination and pharmacological inhibition of specific subsets of the adaptive and innate immune system, we are currently investigating their functional significance in a tumor-stage specific manner. Ultimately, the outcome of these studies may contribute to the improvement of patient survival by shifting therapeutic focus from a cancer cell intrinsic point of view towards a more combined cancer cell intrinsic and extrinsic point of view (Research supported by the Dutch Cancer Society, NKB 2006-3715 and NWO/VIDI 91796307).

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Biocommunication of Cancer Cells from the "Virus first"-Perspective

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Whereas reciprocal cell-cell communication serves as appropriate tool to organize and coordinate growth and development, cancer cells show different behavior. The (i) change in control functions of growth regulation and (ii) the invasion of far reaching tissues in the case of metastasis were long considered to be results of randomly derived damages (mutation) of genetic information. Current knowledge indicates that the genetic content arrangements of organisms strongly depend on viral infection events which doesn't act as lytic disease-causing agents but in most cases as non-lytic persistent viral settlers in both in cellular cytoplasm and in host genomes. Especially the highly colonized mammalian genomes show persistent non-lytic viral settlements represented by both a variety of intact endogenous retroviruses or „defective" retroviral parts such as transposons, retroposons, LTRs, non-LTRs, SINEs, LINEs, group II introns, and other mobile genetic agents. Interestingly some retroviral parts now serve as „effective" modular tools for cellular needs in that the great variety of non-coding RNAs constitute a fine-tuned hierarchy of regulatory functions being essential to all steps and substeps of replication, transcription, translation, repair, recombination and apoptosis. If this highly balanced regulatory network is disturbed, either by microbial infections or by environmental or social stress factors, counterbalanced regulation control can get disregulated and loss of reciprocal biocommunication competence of cells may occur. In this respect carcinogenesis is the result of communication breakdown whereas invasive cancer cells behave accordingly the retroviral-mediated embryological programm of placenta invasion.

Keywords: reciprocal cell-cell communication, persistent viral settlers, cellular key regulations, biocommunication breakdown

Sunday, 5th of July 2009

Sunday-Excursion: to be announced