Albrecht Reichle *Editor*

Evolution-adjusted Tumor Pathophysiology

The Novel Language of Tumor Biology

Springer

Evolution-adjusted Tumor Pathophysiology

Albrecht Reichle
Editor

Evolution-adjusted Tumor Pathophysiology

The Novel Language of Tumor Biology

Springer

Editor
Albrecht Reichle
Department of Hematology and Oncology
University Hospital Regensburg
Regensburg
Germany

ISBN 978-94-007-6865-9 ISBN 978-94-007-6866-6 (eBook)
DOI 10.1007/978-94-007-6866-6
Springer Dordrecht Heidelberg London NewYork

Library of Congress Control Number: 2013942790

Related Subjects

Medicine
Oncology/Hematology
Pharmaceutical technology
Medical ethics
Biological models
Evolution (Biology)
Evolution theory
Evolution history
Biomedicine
Cancer Research
Pharmaceutical Sciences
Evolutionary Biology
Systems Biology
Medicine/Public Health, general
Theory of Medicine/Bioethics
Bioengineering/Social engineering
Translational medicine
Pathophysiology
Philosophy
Diagnostics
Trial design
Communication theory

Contents

Part I
Introduction

Chapter 1
Communication—Evolution—Pathophysiology: An Endogenous Conjunction—Instead of an Introduction

Albrecht Reichle

Abstract The communicative expression of participators in tumor systems, for example, different cell compartments, pathways, oncogenes, tumor suppressor genes, etc., results in the constitution of tumor-immanent normative notions, i.e. tumor-associated immune response, tumor metabolism, etc., and their respective ways of rationalization. The orientation towards more than one read-out 'system' for conceiving rationalizations of tumor-immanent normative notions allows the exemplary investigation of central questions of communication influenced by systems-immanent constraints. Communication processes concertedly express themselves in evolution histories, outcome reports, medical imaging, identification, and quantification of tumor-associated structures and functions, and—last but not least—in the situatively evaluated communicative expression of tumor systems participators. The central task of the current book is to critically scrutinize the automatic transfer of communicative expression—associated with a detectable tumor systems participator—from one tumor system to another. The formal-pragmatic communication theory and the evolution theory shall help find answers to the following critical questions: When can an identical communicative expression of systems participators within different histological or molecular-genetic tumor types (evolutionary-preserved communicative expression) be assumed, and which communicative circumstances are able to alter the communicative expression of identical systems participators in a therapy-relevant manner? Answers to these two questions are important because they may contribute to bridging medical theory and therapeutic practice. Such bridging efforts are embedded in an ethical framework, because therapeutical consequences may be delineated. Evolution-adjusted tumor pathophysiology presents the situatively evaluated constitution of rationalization processes for tumor-promoting normative notions, and, thus, a novel therapeutically accessible level for overcoming cytogenetically and molecular-genetically based tumor heterogeneity.

A. Reichle (✉)
Department of Hematology and Oncology, University Hospital Regensburg,
93042 Regensburg, Germany
e-mail: albrecht.reichle@klinik.uni-regensburg.de

A. Reichle (ed.), *Evolution-adjusted Tumor Pathophysiology,*
DOI 10.1007/978-94-007-6866-6_1,

Introduction

The clinical efficacy of combined modularized (biomodulatory) therapies for metastatic tumors together with observations of distinct cell compartments and their capacity to initiate tumor growth in heterologous cell types provide excellent opportunities to point to central communication problems among tumor systems participators.

For pragmatic purposes, communication primarily turns all tumor systems participators into abstract and scientifically assignable 'artifacts' that transmit information and concertedly constitute communicative expression of tumor systems via physically accessible tumor-immanent rationalization processes. Evolutionarily organized rationalization processes for shaping tumor-immanent normative notions provide functions, such as angiogenesis, inflammation, immune response, etc., but also decision maxims (hubs, nodes) and tumor-associated molecular or morphological structures.

In particular, the 'metabolism' of tumor evolution cannot be operationalized without the inclusion of stringent ideas on how biological communication processes are realized in developing tumors. Also theories on evolution-historical processes have to consider the fact that communication is the medium by which evolutionary processes are promoted, even if communication is assumed to be unidirectional in Darwinian 'selection processes' and selection aims at arbitrarily chosen normative notions.

The extensive and so far not systematically organized material on the novel tumor pathophysiology compelled to an exploratory approach, guided by a formal-pragmatic communication theory. The main goal of this theory is to provide instruments for uncovering the rules underlying the organization of the communicative expression of systems participators and the therapeutic modulation or redirection in steadily evolving biologic systems, such as tumors.

The communicative expression of tumor systems participators results in the constitution of tumor-immanent normative notions, i.e. tumor-associated immune response, tumor metabolism etc., and their respective ways of rationalization.

The orientation towards more than one read-out 'system' for conceiving rationalizations of tumor-immanent normativity allows the exemplary investigation of the central questions of communication influenced by systems-immanent constraints, such as evolutionarily restricted or diversified communication-derived rules, the multifaceted types of communication within tumor diseases, and evolutionarily based intersystemic exchange processes. In combination, these factors concertedly express themselves in evolution histories, out-come reports, medical (molecular) imaging, the identification and quantification of tumor-associated structures and functions, and—last but not least—in the situatively evaluated communicative expression of tumor systems participators provided by the systems context for generating tumor-immanent normative notions.

The contradictions between the phenomenology of an individual tumor disease and methodologically offered scientific explanations are uncovered by a more sharpened and diversified view on the single lines of traditions that prefer particular forms

of scientific perception for comprehending communicative expression of systems participators. The different perspectives are indicated by the selection of respective read-out systems.

Usually, we assume that functions of molecular-genetic and genetic aberrations in tumors may be simply added up or interconnected in a systems-biological manner without acknowledging their evolutionarily confined situative communicative expression in distinct systems stages. Upon closer examination, this 'modus operandi' is frequently less successful in explaining the natural history of a tumor disease. In daily clinical practice, theoretical explanations often prove to be contrary to the observed natural history of a tumor disease.

In tumors, systematic reconstructions of the communicative expression of situative systems participators may allow a better understanding of the seemingly irresolvable nexus between theory and practice.

Because the discussed results of the combined modularized therapies for metastatic tumors are not common knowledge, data on clinical trials including combined modularized therapies are required. Showing that the tradition of reductionist data interpretation is insufficient for explaining the concerted activity of drug components with poor or no single agent activity is rather simple. However, this conjuncture is not important, because the theoretical and practical methodological instruments discussed for reconstructive activities may be generalized and also used in a different biological context.

The point is: no refutation of reductionist-derived considerations and their application in an evolutionary context. Ideas for explaining communicative processes in biology and their principles of organization, exemplified by the two different pillars of evolution history and evolution theory, originate from rather diverse scientific disciplines. These ideas should be reconstructed and operationalized to constitute an evolution theory that explains the 'metabolism' of evolution.

Traditional evolution historical considerations may neither sufficiently explain the activity profiles of combined modularized therapies nor the clinical hints that such therapy approaches have the capacity to induce a therapeutically relevant biological memory for long-term tumor control; therefore, the focus inevitably turns to evolution theories. Simultaneously, the data show to what extent the scientific history of data interpretation is shaped by traditional patterns of recycling reductionist thinking. Such patterns remain in the collective memory to be transformed and adapted in due course to changing interests and specific therapeutic purposes. To some extent, such adaptations are 'distortions', because originators are unable to foresee how the after-world is going to deal with their conceptions. Vice versa, a novel conception for describing the 'metabolism' of evolution and its successful application in a formal-pragmatic communication theory may confirm the continuance and necessity of the original reductionist considerations.

It is in our interest to comprehend the therapeutically all important situative validity and denotation of systems participators within the evolutionarily developing novel contexts beyond the multifaceted communicative behavior of tumor systems participators. Here, the hermeneutic approach is used for highlighting ways how to systematically reconstruct rationalizations of tumor-immanent normative notions

for diagnostic and therapeutic purposes and for appointing the situative function of tumor systems participators within a concrete rationalization process that is assigned to propagate a distinct tumor-associated normative notion.

When we turn away from the myriads of historical descriptions of evolution and try to address ourselves to the theoretical considerations on evolution, i.e. to the 'metabolism' of evolution and the reconstruction and modulation of tumor-immanent normative notions, we reductionistically undermine the multifaceted evolution histories with the aim to comprehend communicative rules to which evolutionary processes adhere.

The process that initiates the constitution of an evolution theory requires the involvement of multifold scientific disciplines, whereas the theory itself should be self-explanatory. My own starting point to converge multifold scientific disciplines to evolution theory is internal medicine. Based on the diagnostic and therapeutic equipment of a physician, I tried to study the whole array of questions evolving between the conflicting priorities of medical theory and therapeutic practice and between evolution history and evolution theory. Most investigators may feel that these questions are best answered by consulting classic reductionistically working systems biology. The fact that, in the present case, a physician dares to investigate such questions is derived from systematic therapeutic experiences in combined communicative interactions with tumor-promoting systems participators. Examples are given in the current book: Tumor systems are accessible for communicative interactions by modulating and redirecting tumor-immanent normative notions.

The justification for the committed systematic transgression to other neighboring and supplementing scientific fields, including philosophy, lies in the nature of the investigated tumor systems objects and their inevitable integration and organization within tumor-immanent rationalization processes to constitute tumor-associated normative notions.

Therapeutically aligned communication with tumor systems does not only mean launching or interrupting information processes, but equally focuses on the communicative expression of tumor systems participators and the specified and individualized shaping of tumor-associated normative notions. Therefore, redirecting and modulating the communicative expression of systems participators may be a highly efficacious and clearly specifiable therapeutic goal. Furthermore, combined modularized therapies help to detect multifaceted and situatively adapted rationalization processes available for ubiquitously occurring tumor-immanent normative notions.

Artists and writers as well as their audience always have the privilege and proclivity to feel completely free from constraints imposed by single disciplines and highly sophisticated niches. The unconditional use of rather diverse scientific fields is required for uncovering the situative validity and denotation of tumor systems objects in an evolutionary context, i.e. the situative communicative expression of tumor systems objects, beyond the simple proof of 'artifacts', their identification, quantification, and suggestion of communicative expression 'per se'. Such uncovering contributes to the permanent evolution-immanent transformation of provable tumor systems objects to corresponding systems subjects that are characterized by

their systems-imposed, communication-derived situative validity and denotation as a display of their evolutionary-based communicative expression.

At that stage, the exclusively communication-related tumor systems subject with its situatively inherent communicative expression becomes the center of scientific interest.

The attempt of a multidisciplinary integrative approach—that exceeds boundaries drawn by multifold scientific niches that develop either unwarrantedly or rather justifiably—offers the opportunity to investigate the transformation processes between medical theory and therapeutic practice as well as between objects and systems subjects. Interdisciplinarity provides and organizes the methodological instruments for routinely reconstructing evolutionarily initiated transformations and for therapeutically using this novel information that is now summarized in evolution-adjusted tumor pathophysiology.

Multidisciplinarity is the adequate approach to converging the transformation problem. However, besides daily medical practice, multidisciplinarity includes communication theory, philosophy, molecular biology, systems biology, bioinformatics, genetics, etc. Thus, this approach may involve the risk of inadequately covering all neighboring scientific fields affecting evolution-adjusted tumor pathophysiology. In such cases, I would like to ask my readers to kindly overlook any oversights or inaccuracies.

This book is organized from 'bed side' to 'bench', corresponding to the 'historical' time line: (1) Combined modularized therapies for metastatic tumors are pointing to central problems of communication among 'systems participators' in tumors and may efficaciously address the therapeutic problems arising from genetically based tumor heterogeneity. (2) A communication theory provides the basis for explaining social engineering either endogenously within the natural evolutionary tumor process or by implementing non-normative boundary conditions with combined modularized therapies. (3) Observations from rather different disciplines are a prerequisite for reconstructing and operationalizing starting points for an evolution theory, and (4) for developing an evolution theory that is borne by evolution-adjusted tumor pathophysiology and that (5) aims at uncovering the 'metabolism' of evolution. As a direct consequence, tumor staging focuses on rationalization processes, the non-genetic counterpart of the genome. (6) Data on systematic reconstructions of tumor-immanent normative notions, which can be depicted in rationalization processes, are the basis of communication-derived tumor pathophysiology. Systematic descriptions of rationalization processes pave the way from a genome-centric to a rationalization-centric, namely evolution-adjusted tumor-pathophysiology. (7) The introduction of evolution-adjusted tumor pathophysiology represents a prerequisite for diversifying therapeutic instruments aimed at improving palliative care and personalizing tumor therapy. (8) Combined modularized therapy approaches, a description of tumor biology based on evolution-adjusted pathophysiology, and novel tools of biomarkers will allow the adaptive bioengineering of tumor response. (9) Evolution-adjusted pathophysiology provides a novel reification of the scientific picture about the 'objective' world by objectifying the subjectivity of systems objects in biological systems.

Following these general explanations on methodological issues, some remarks should be given on the claim for evolution-adjusted tumor pathophysiology, which may be established for the routine evaluation of the communicative expression of systems participators.

Bridging medical theory and therapeutic practice is a timeless challenge, and the success of bridging depends on the situative circumstances, traditions, and emancipatory interests. Mostly, scientists do not sufficiently acknowledge that medical knowledge is based on methodological issues of comprehension, particularly in the field of basic medical sciences, i.e. pathology, pathophysiology, molecular-genetics, and biochemistry. These disciplines are always based on medical theories that tend to be steadily recycled in daily practice.

Based on the tendency to recycle patterns of medical thinking, results gained from basic science may quickly reach the status of facticity, both intentionally and unintentionally. This status means that results derived from arbitrary biologic systems, particularly from successfully established model systems, are generalized without hesitation and transferred into newly arising biological systems contexts, as in the case of tumor diseases.

The substantiation of tumor systems objects is promptly followed by reckoning distinct 'historical' communicative expressions or generalized communicative expressions 'per se'. The catchphrase is 'from bench to bed side'. Yet, the question arises: What is the situative communicative expression of a few familiar molecular-genetic aberrations detected in tumor cells on the background of an arbitrary number of additional aberrations in tumor and stroma cells and genetically based tumor cell heterogeneity?

Pathology, molecular-pathology and cytogenetics allow the easy detection of specific tumor heterogeneities. In contrast, the current pathophysiology is overwhelmingly a theoretically-based science, and most pathophysiological case-related phenomena are only poorly integrable in daily clinical practice.

The central task of the current book is to critically scrutinize the automatic transfer of the communicative expression of tumor systems participators from one tumor system to another—even within tumor systems accomplishing identical normative notions. Formal-pragmatic communication theory and evolution theory shall help find answers to the following critical questions: When can an identical communicative expression of systems participators within different histological or molecular-genetic tumor types (evolutionary preserved communicative expression) be assumed, and which communicative circumstances are able to alter the communicative expression of identical systems participators in a therapy-relevant manner?

Attempts to detect the 'technical' prerequisites for the communicative expression of tumor systems participators reach ethical relevance: Bridging medical theory and therapeutic practice, the development and use of methodologies for reconstructing situative communicative expression of tumor systems objects within multifaceted, evolution-based systems contexts, and consequentially the purposeful modulation and redirection of tumor-associated normative notions related to tumor progression—an up-coming novel field of palliative care—are medical procedures embedded in an

ethical background. Insofar, it seems to be justified to systematize the communicative expression of systems objects, particularly rationalization processes, on the basis of situatively evolving communicative contexts that have been investigated in an equal manner. Consequently, the need arises for a systematic presentation of evolution-adjusted tumor pathophysiology as a novel language of tumor biology that may be integrated into daily routine diagnostics.

Evolution-adjusted tumor pathophysiology presents the situatively evaluated constitution of rationalization processes for tumor-promoting normative notions and, thus, a novel therapeutically accessible level for overcoming cytogenetically and molecular-genetically based tumor heterogeneity.

After these general considerations on communication, evolution, and tumor pathophysiology, I would like to thank all persons, who contributed to the publication of this book in rather different ways. G. Haegeman supported our efforts to proceed with combined transcriptional modulation in combination with metronomic low-dose chemotherapy to redirect and modulate tumor-immanent normativity for attenuating tumor growth.

My special thanks go to all the scientists and the steadily growing community of clinicians who participated in the large number of clinical phase II trials on biomodulatory therapies and to those scientists who contributed to a chapter to give the issue novel input. Ms Schoell, I want to thank for her excellent linguistic support.

The pragmatic considerations of J Habermas on communication theory inspired the systematic interpretation of the data acquired during combined modularized therapies in metastatic tumors and built the basis for formulating an evolution theory.

This book is dedicated to all students who have decided to become physicians. Famous clinical scientists and their invaluable experience do not lose their standing or charisma if we ask that the gap between medical theory and therapeutic practice should be methodologically supplemented and systematized by evolution-adjusted tumor pathophysiology to generate replicable knowledge on evolutionarily confined communicative expression with the aim to further foster the personalization of tumor therapy: Standard operating procedures are generated to further the knowledge of physicians in rather different medical fields. However, such knowledge should represent a continuous basis and challenge to methodologically bridge the conflicting poles, i.e. medical theory and therapeutic practice.

Both young physicians and basic scientists should be stimulated by the book to promote their own research—with the necessary openness to risk—for the further methodological integration of medical theory and therapeutic practice as a perpetual task in the field of evolution-adjusted tumor pathophysiology and translational medicine.

Part II
Combined Modularized Therapies for Metastatic Tumors: Pointing to Central Problems of Communication Among 'Systems Participators' in Tumors

Chapter 2
Applied Systems Biology for the Control of Metastatic Cancer: Therapeutic Top-Down Strategy for Targeting the Tumors' Normativity

A. Reichle and G. C. Hildebrandt

Abstract We hypothesized, that tumor systems-directed therapies might have the capability to therapeutically modulate and redirect the tumor systems' stability, homeostasis, robustness, and normative notions. This therapeutic 'top down' strategy may provide novel targets for the control of metastatic tumor disease. We comparatively analyzed redirection and modulation of tumor-associated normative notions, particularly inflammatory, osteoblastic activities, ECOG status, and metastatic potential in parallel with response, time to response and duration of response induced by continuously administered biomodulatory treatment modules (module M: metronomic low-dose chemotherapy; module A: pioglitazone plus etoricoxib; module A+M; module A+M/+: plus second transcriptional modulator [interferon-alpha or dexamethasone +/− imatinib or dexamethasone plus lenalidomide]) in the metastatic stages of seven different histological tumor types (ten phase II trials, two of them randomized; 333 patients; 80 % systemically pre-treated). A series of (randomized) phase II studies demonstrated differentially modularized accessibility of tumor-associated normative notions, i.e., inflammation, ECOG status, osteoblastic metastases, and metastatic tumor spread for mediating objective tumor response. Biomodulatory treatment schedules may induce long-term disease stabilization followed by prolonged objective response (3–100 %), even continuous complete remission, despite poor or no monoactivity of the respective drugs. Progression-free survival data are comparable with those of reductionist-designed standard first-line therapies. The differential response patterns indicate the therapies' systems biological activity. Clinical efficacy of 'top-down' therapy strategies (biomodulatory therapy elements administered as fixed modules) for metastatic cancer provide excellent opportunities to point to central problems of communication among 'systems participators' in tumors. Combined modularized therapies (1) help to detect multifaceted, situatively adapted rationalization processes available for ubiquitously occurring

A. Reichle (✉)
Department of Hematology and Oncology, University Hospital Regensburg,
93042 Regensburg, Germany
e-mail: albrecht.reichle@ukr.de

G. C. Hildebrandt
Division of Hematology and Hematologic Malignancies, Huntsman Cancer Institute,
University of Utah School of Medicine, 2000 Circle of Hope, Salt Lake City,
UT, 84112–5550, USA

A. Reichle (ed.), *Evolution-adjusted Tumor Pathophysiology,*
DOI 10.1007/978-94-007-6866-6_2, © Springer Science+Business Media Dordrecht 2013

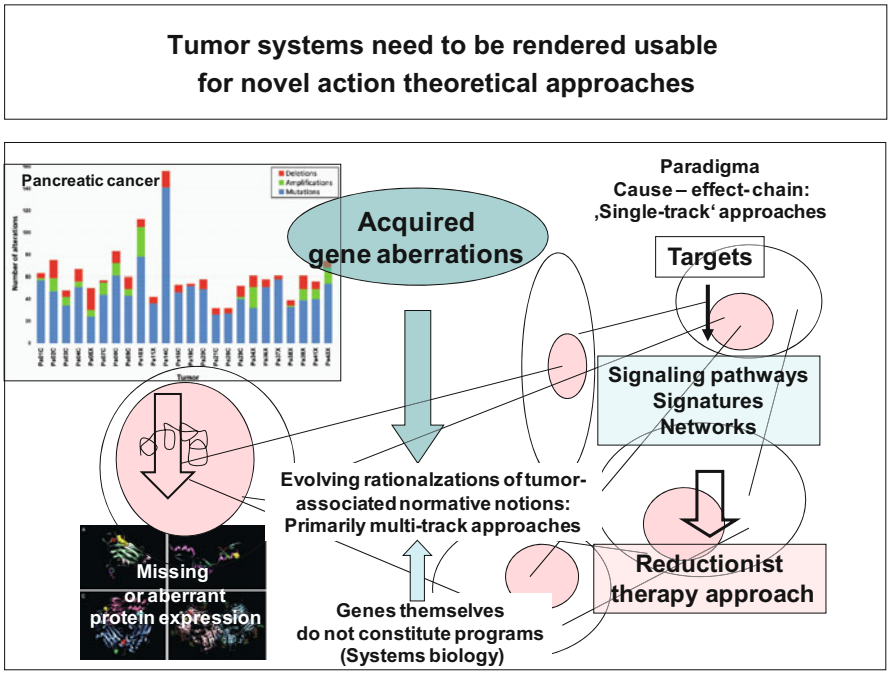


Fig. 2.1 The commonly used 'bottom-up' strategy regards as sufficient the availability of targets in cellular tumor compartments without identifying validity and denotation of targeted, presumably tumor-promoting systems participators. The communicatively cross-linked 'background', which may be functionally specified due to varying numbers of chromosomal or molecular-genetic aberrations, remains therapeutically unrecognized

tumor-immanent normative notions, (2) may uncover novel regulatory systems in tumor biology (e.g., hubs), (3) pathologies within communication processes (e.g., inconsistencies, disturbances in intersystemic exchange processes) (4) are a basis for studying communicative rules mediating the 'metabolism' of tumor evolution, and (5) may pave the way for inducing biological memory in metastatic tumors.

Keywords Metastatic tumors · Applied systems biology · Combined modularized tumor therapy · Evolution theory · Evolution-adjusted tumor pathophysiology

Introduction

Tumor-related activities that seem to be operationally induced by the diversity of tumor-immanent normative notions and their multifaceted evolutionary confined rationalization processes, such as normative functions (i.e. inflammation, neoangiogenesis, Warburg effect, immune response, extracellular matrix remodelling, cell

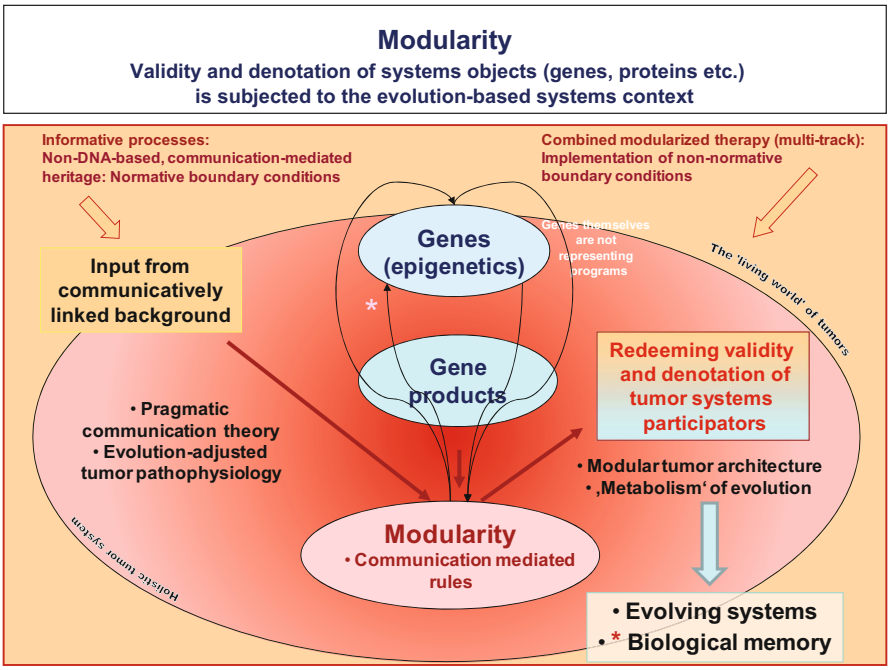
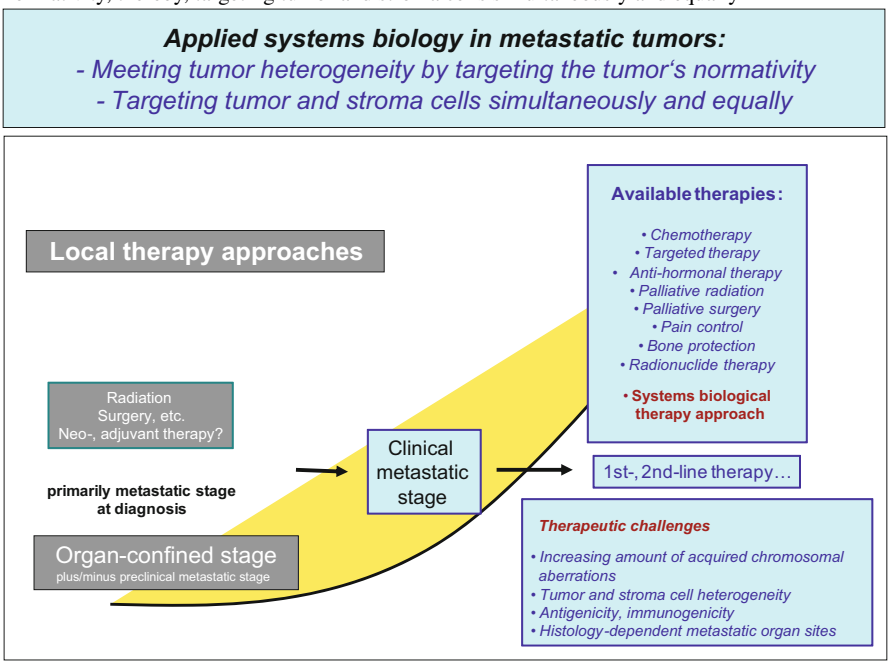


Fig. 2.2 Tumors allow experimental therapeutic access from inside in a comprehensive and reconstructive way (systems view) via modular (biomodulatory) therapy approaches and may be described as evolutionary developing systems. Modular therapies evolve the informative background, which redeems validity and denotation of tumor-associated objects. Therapeutically accessible pathologies may derive from the decoupling of functional cellular and systems 'world' and can be targeted by modular therapy approaches

proliferation rate, apoptosis, coagulation effects), normative structures and decision maxims (hubs), present itself from a systems perspective as an enhancement of complexity. So far, tumor systems have been assumed to defy experimental therapeutic access from inside, in a comprehensive and reconstructive way that means, in a communication-derived systems view, and to only comply with reductionist knowledge with regard to biochemical pathways (Fig. 2.1).

We hypothesized, that tumor systems-directed therapies might have the capability to use aggregated action effects of tumor-immanent normative notions, as adjustable sizes to therapeutically modulate and redirect the tumor systems' stability, homeostasis, robustness, and normative notions, and that this therapeutic 'top down' strategy may provide novel targets for the control of metastatic tumor disease in contrast to currently provided 'bottom-up' strategies including the classic 'targeted' therapy approaches: Combined modularized therapy approaches have been designed to study the operative accessibility of tumor-immanent normative notions for tumor control (therapeutic implementation of 'non-normative' boundary conditions into the tumor systems world) by ubiquitously available, non-oncogene addicted, but differentially distributed targets among tumor and stroma cells [1–6] (Fig. 2.2, Tables 2.1, 2.2).

Table 2.1 During progression from the organ-confined stage to the clinical metastatic stage tumors acquire asynchronously multifold chromosomal and molecular-genetic aberrations. Applied systems biology in metastatic tumors may meet this therapeutic challenge by targeting the tumor's normativity, thereby, targeting tumor and stroma cells simultaneously and equally



Materials and Methods

We comparatively analyzed redirection and modulation of tumor-associated normative notions, particularly inflammatory, osteoblastic activities, ECOG status, and metastatic potential in parallel with response, time to response and duration of response induced by continuously administered biomodulatory treatment modules (Table 2.4, 2.5) (module M: metronomic low-dose chemotherapy; module A: pioglitazone plus etoricoxib; module A+M; module A+M/+: plus second transcriptional modulator [interferon-alpha or dexamethasone +/− imatinib or dexamethasone plus lenalidomide]) in the metastatic stages of different types of tumors (ten phase II trials, two of them randomized; 354 patients; 80 % systemically pre-treated; metastatic melanoma (two trials, one randomized), (angio-) sarcoma, renal clear cell carcinoma (two trials), glioblastoma, castration-resistant prostate cancer (two trials on CRPC), gastric cancer (randomized phase II trial), multi-systems Langerhans' cell histiocytosis, and multiple myeloma in third-line) (Tables 2.3, 2.6) [7–22].

Further, we analyzed the follow-up of patients discontinuing study medication due to medical indications, and who achieved objective response to module A+M/+combined with a second transcriptional modulator (dexamethasone), besides metronomically administered imatinib (400 mg once daily) in CRPC (phase

Table 2.2 The 'Top-down' approach allows redirecting and modulating the communicative 'background', which mediates validity and denotation of tumorpromoting systems participators and organizes the constitution of rationalizations for maintaining tumor-immanent rationalizations. The 'background' is modularly arranged and therapeutically accessible with primarily multi-track, modularized therapy elements

Studies' objective: *Meeting tumor heterogeneity in metastatic tumors, high therapeutic efficacy and a low rate of toxicity by applied systems biology*

'Top-down' approach	*Communication-related targets*
Redirecting the communicative expression of tumor-promoting systems participators *communication lines, pathways etc.*	**Tumors' normativity beyond the 'hallmarks' of cancer:** - *Tumor-immanent normative structures* - *Normative functions* - *Decision maxims (hubs)*
Therapeutic modulation of the communicative 'background' *Multi-track, combined modularized tumor therapy*	**Modular access to the tumors' normativity:** - *Osteoblastic processes (prostate cancer)* - *Tumor angiogenesis* - *Tumor-promoting inflammation* - *Tumor-associated immune escape* .....
Novel tool of therapeutic targets, drugs *Ubiquitously accessible targets in tumor and stroma cells* ***Combined transcriptional modulation:*** *Induction of epigentetic changes*	**Non-oncogene addicted targets** - ***COX-2, PPARbeta*** *(etoricoxib)* - *PDGF-R (imatinib); targets of lenalidomide* - ***Regulatory T-cells etc.*** *(metronomic low-dose chemotherapy)* - ***PPAR alpha/gamma receptors*** *(pioglitazone)* - ***Glucocorticoid receptor*** *(dexamethasone) or* ***interferon-alpha receptor*** *(interferon-alpha)*

I/II trial for CRPC, first-line therapy) or lenalidomide (10 or 15 mg once daily) in multiple myeloma (third-line therapy for MM, phase I, on-going phase II trial) (Chap. 19).

Results

A series of (randomized) phase II studies demonstrated differentially modularized accessibility of tumor-associated normative notions, i.e., inflammation, ECOG status, osteoblastic metastases, and metastatic tumor spread for mediating objective tumor response. Biomodulatory treatment schedules may induce long-term disease stabilization followed by prolonged objective response (3–100 %), even continuous complete remission, despite poor or no monoactivity of the respective drugs (Table 2.7). Progression-free survival data are comparable with those of reductionist-designed standard first-line therapies. The differential response patterns indicate the therapies' systems biological activity (Figs. 2.3, 2.4 and 2.5).

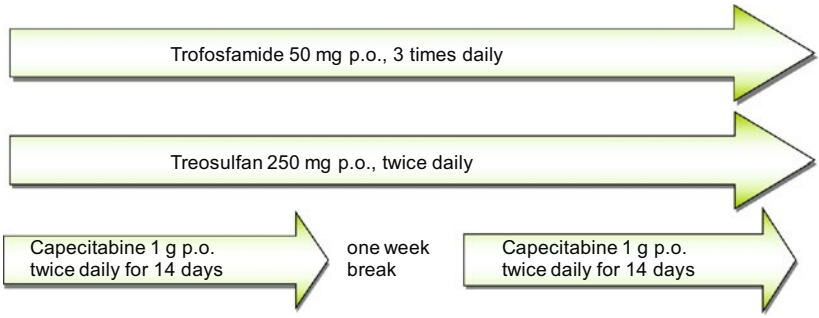
Table 2.3 For studying the capacity of combined modularized tumor therapies to redirect the tumors' normativity, we selected tumors as normative model systems, i.e., tumors with predominant pro-angiogenic component, with strong pro-inflammatory component, and tumors with pro-inflammatory characteristics in the metastatic stage

Tumors as normative model systems:
Combined modularized therapy: Antiangiogenetic/ anti-inflammatory/immun-modulatory trials

- **Tumors with high vascular density**
  - Angiosarcoma
  - Renal clear cell carcinoma (RCCC)
- **Tumors with extensive inflammation**
  - Refractory multivisceral Langerhans' cell histiocytosis (mLCH)
  - Multiple myeloma (MM)
- **Tumors with inflammation in advanced stage**
  - Sarcoma
  - Melanoma
  - Cholangiocellular carcinoma (CCC)
  - Castration-resistant prostate cancer (CRPC)
  - Gastric cancer
  - Glioblastoma

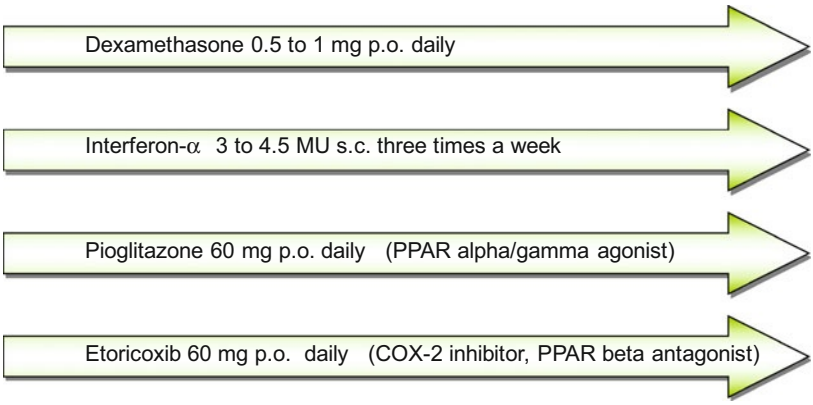
Table 2.4 Metronomic low-dose chemotherapies and mechanisms of action

Angiostatic, immunmodulatory and anti-inflammatory therapies: Metronomic low-dose chemotherapies



Angiostatic:	*Up-regulation of thrombospondin 1, reduction of circulating endothelial cells, decreased recruitment of endothelial progenitor cells, and blocking rebounds by the tumor vasculature*
Anti-inflammatory	*in gastric cancer*
Immun-regulatory:	*Reduction of tumor-induced immune-tolerance, enhanced immunity against tumor antigens, and strongly curtails immunsuppressive regulatory T-cells*

Table 2.5 Targeting the tumor systems biology: Combined transcriptional modulation of ubiquitously available targets



- **Pioglitazone/etoricoxib** (Metastatic melanoma, cholangiocellular carcinoma, sarcoma, multivisceral Langerhans' cell histiocytosis, gastric cancer, glioblastoma)
- **Combined transcriptional modulation**
  - Pioglitazone/dexamethasone/etoricoxib (Castrate-resistant prostate cancer)
  - Pioglitazone/dexamethasone (Multiple myeloma)
  - Pioglitatzone/interferon-alpha/etoricoxib (Renal clear cell carcinoma)

Table 2.6 The table gives an overview about the performed combined modularized therapy approaches. In three trial designs we used combined transcriptional modulation (castration-resistant prostate cancer, multiple myeloma and renal clear cell carcinoma)

Experimental plan: Combined modularized tumor therapy (n= 354 patients, 19 centers)
(Reichle A, Cancer Microenvironment, 2008; Reichle A, J Clin Oncol 29: 2011 (suppl; abstr 4599), Reichle A, Blood suppl. ASH 2012)
o pioglitazone, **d** selective COX-2 inhibitor, dexamethasone, *interferon-a, PPAR= peroxisome proliferator-activated receptor agonist

Metastatic cancer: Tumor type	Metronomic low-dose chemotherapy	No. of patients	*Receptor agonist/antagonist* PPARa/γ agonist[o]	PPARδ antagonist[Δ]	Gluco-corticoid[d]	IFN-α *	Publications
Kaposi sarcoma	Trofosfamide	1	+	+	-	-	*Arch Dermatol, 2004*
(Hem)angiosarcomas	Trofosfamide	12	+	+	-	-	*Cancer, 2003/04*
Sarcomas I	Trofosfamide	21	+	+	-	-	*Cancer, 2004*
Melanoma I	Trofosfamide	19	+	+	-	-	*Cancer, 2004*
Melanoma II Arm M		35	-	-	-	-	*Melanoma Research, 2007*
Arm A/M		32	+	+	-	-	*Lancet Oncol 2007 (comment) Cancer Microenvironment 2008, 2009*
Langerhans' cell histiocytosis	Trofosfamide	3	+	+	-	-	*Br. J.Haematol, 2005*
Glioblastoma	*Capecitabine*	14	+	+			*Oncology, 2007*
Renal clear cell carcinoma (A/M)	*Capecitabine*	18	+	+	-	-	*Biomarker Insights, 2006*
Renal clear cell carinoma (A/M+)	*Capecitabine*	33	+	+	Combined transcriptional modulation	+	*World J Urol, 2012 Biomarker Insights, 2006*
Castration-refractory prostate cancer	Treosulfan *Capecitabine*	61	+	+	+ (imatinib)		*ASCO abstract, 2007; 2011*
Multiple myeloma	Treosulfan	36	+	+	+	-	*Lancet Oncology, 2006*
Cholangiocellular carcinoma		6	+	-	+ (lenalidomide)	-	Blood 2012; **120**: 5029
		21	+	+	-	-	*From molecular to modular tumor therapy*
			+	+	-	-	
Gastric c. Arm M	*Capecitabine*	42	-	-	-	-	*ASCO abstract 2009*
Arm A/M	*Capecitabine*		+	+	-	-	