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

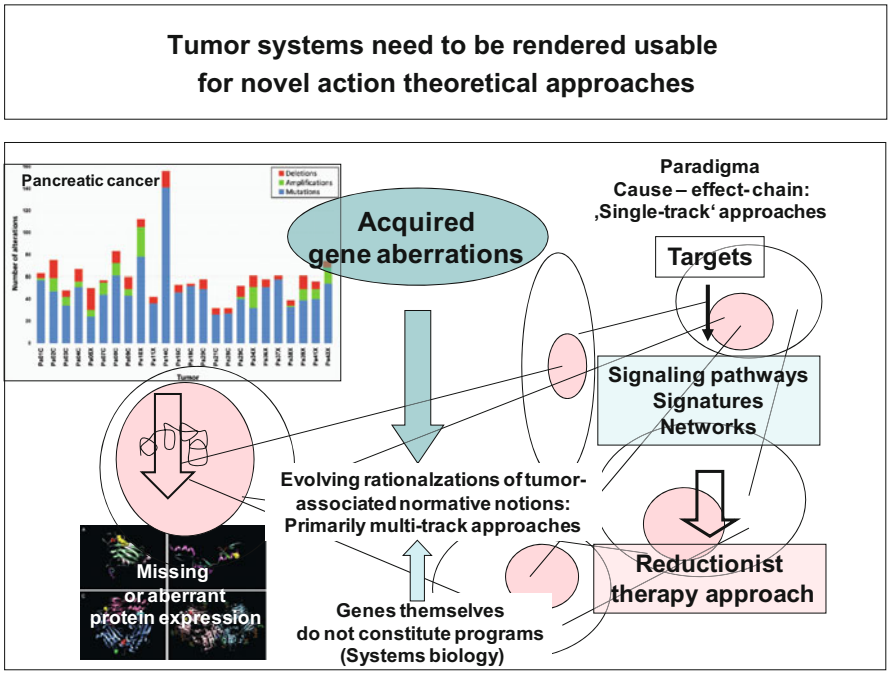


Fig. 2.1 The commonly used 'bottom-up' strategy regards as sufficient the availability of targets in cellular tumor compartments without identifying validity and denotation of targeted, presumably tumor-promoting systems participators. The communicatively cross-linked 'background', which may be functionally 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

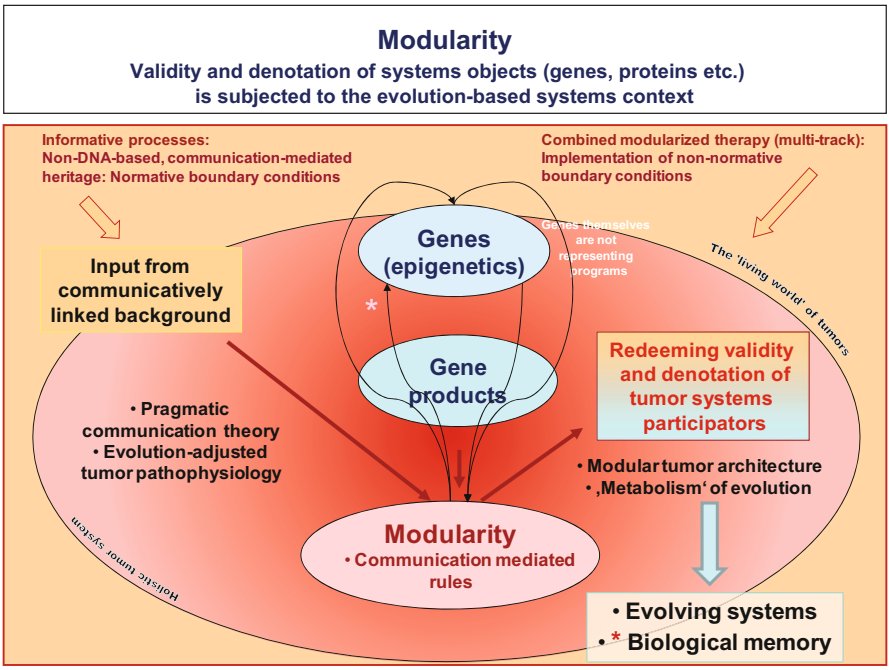
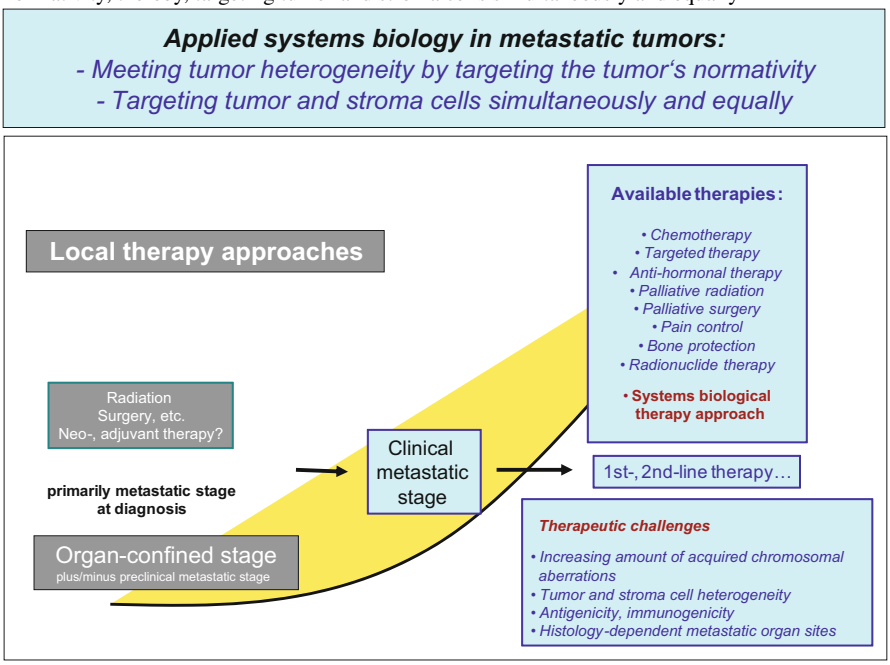


Fig. 2.2 Tumors allow experimental therapeutic access from inside in a comprehensive and reconstructive way (systems view) via modular (biomodulatory) therapy approaches and may be described as evolutionary developing systems. Modular therapies evolve the informative background, which redeems validity 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).

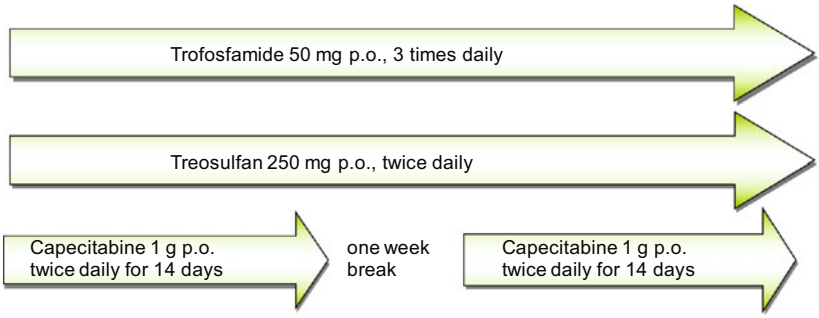
Table 2.3 For studying the capacity of combined modularized tumor therapies to redirect the tumors' normativity, we selected tumors as normative model systems, i.e., tumors with predominant pro-angiogenic component, with strong pro-inflammatory component, and tumors with pro-inflammatory characteristics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

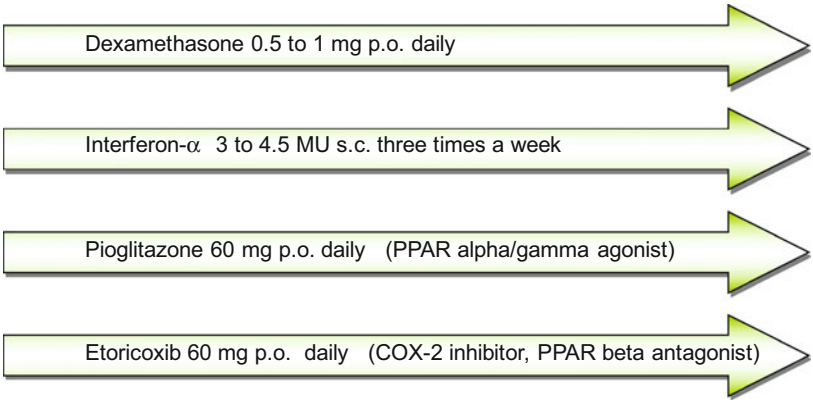
Table 2.4 Metronomic low-dose chemotherapies and mechanisms of action

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	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*		+	+	-	-	

Table 2.7 Overview of outcome following combined targeting of the modular tumor architecture in pre-treated patients (80 %)

Combined targeting of the modular tumor architecture in pre-treated patients (80%):Response behavior (n=321)

(Reichle A, Cancer Microenvironment, 2008; Reichle A, J Clin Oncol 29: 2011 (suppl; abstr 4599), Reichle A, Blood suppl. ASH, 2012)

Tumor types (n=9)/Therapy arm	Response			
	No. of patients	partial remission/ PSA response %	complete remission %	continuous CR %
Sarcomas I	21	19%	16%	**5%**
Angiosarcomas/Hemangiopericytomas/Kaposi s.	8/4/1	12%/25%/100%	62%/0%/0%	**12%/0%/0%**
Melanoma Arm M (R)	35	3%	0%	**0%**
Arm A/M (R)	32	9%	3%	**3%**
Langerhans' cell histiocytosis (multivisceral)	3	-	100%	**100%**
Renal clear cell carcinoma I (RCCC)	18	0%	0%	**0%**
Renal clear cell carinoma II (plus IFN-a)	33	35%	13%	**9%**
Castration-refractory prostate cancer (CRPC)	36	41%	0%	**>4 years minimal residual disease**
CRPC (plus imatinib)	61	37.7%	0%	**>5 years minimal residual disease**
Cholangiocellular carcinoma	21	24%	5%	**5%**
Multiple myeloma (plus lenalidomide, third-line, phase I)	6	67%	17%	**17%**
Gastric cancer Arm M (R)	20	20%	0%	**0%**
Arm A/M (R)	22	14%	0%	**0%**

Toxicities of combined modularized therapies were manageable by early dose reductions according protocol in case of grade 2 toxicities, and therefore, facilitate long-time administration of study therapy. Only 3 % of patients permanently discontinued therapy due to site effects ([7, 23], Chap. 5). Long-term tumor control can be achieved in elderly (up to 86 years) and medically non-fit patients (Chap. 5) on the basis of moderate treatment-related toxicity, particularly less grade 3 and 4 toxicities.

Tumor-specific and stage-specific therapeutic accessibility of inflammation-related processes to induce response in all tumor types indicate a constitutive spin-off of novel rationalized systems functions during the metastatic process [24]. Furthermore, this accessibility shows differential integration of inflammation processes into the context-dependent 'living world' of tumor compartments that is marked by tumor-specific and subtype-specific rationalization processes: Inflammation-related activities are communicatively promoted and differentially adapted during tumor evolution. Empirically, differences may be detected in the modalities of developing evolutionary systems and in the acquired functional impact of inflammation-related systems [24].

The observed response patterns, either very rapid or delayed tumor responses, indicate that communicative inconsistencies may be therapeutically met (Achilles' heels). Disturbances in intersystemic exchange processes are suggested, if biomarkers (e.g., C-reactive protein) or signatures depicting the redirection of normative

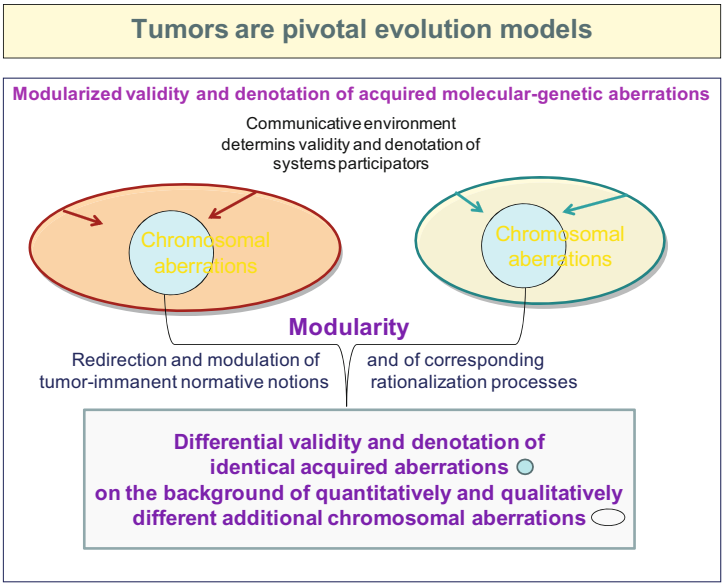


Fig. 2.3 Tumors represent pivotal evolution models, as the communicative 'background' of tumor-promoting systems objects is highly variable due to the varying numbers of chromosomal or molecular-genetic aberrations, which individualize a tumor disease to a high degree. But likewise, rationalizations of tumor-immanent normative notions are individualized and differentially accessible by modularized therapy approaches

notions (here tumor-associated inflammation) show a low sensitivity to predict clinical benefit [24].

Temporally limited metronomically administered, combined modularized therapies may facilitate biological memory for stably sustaining long-term tumor growth control (12.5–15 months) without disease specific therapy in patients, who discontinued study medication due to non-tumor-related surgical interventions (Chap. 19).

Differential approaches implementing combined transcriptional modulation plus metronomic chemotherapy demonstrated the capacity to redirect and modulate tumor-immanent normative functions in a multifaceted way (inflammation control, anti-osteoplastic effect, immunregulation, biological memory, induction of continuous complete remission; long-term maintenance at minimal residual disease), in renal clear cell carcinoma, multiple myeloma and castration-resistant prostate cancer (Tables 2.7, 2.8, Chap. 19). Targeting the tumors' normativity by combined transcriptional modulation allows to diversifying therapeutic instruments for purposive rationale therapies with the aim to specify palliative care (Chap. 15).

Metastatic lesions, pretreated with palliative radiotherapy, had frequently shown local progression in the radiation field (86 % of $n = 56$ previously locally irradiated patients), despite disease stabilization or response towards combined modularized therapies at other metastatic tumor sites.

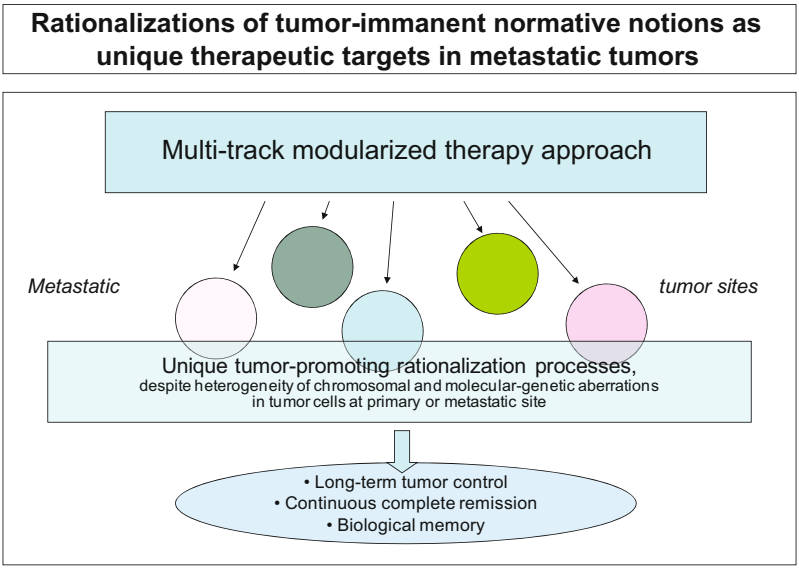


Fig. 2.4 Induction of long-term tumor response or continuous complete remission in metastatic tumors indicates that tumor-promoting rationalizations at the metastatic sites are uniquely constituted within an individual tumor disease and are efficacious targets for combined modularized tumor therapies to overcome cytogenetic heterogeneity in tumor cells

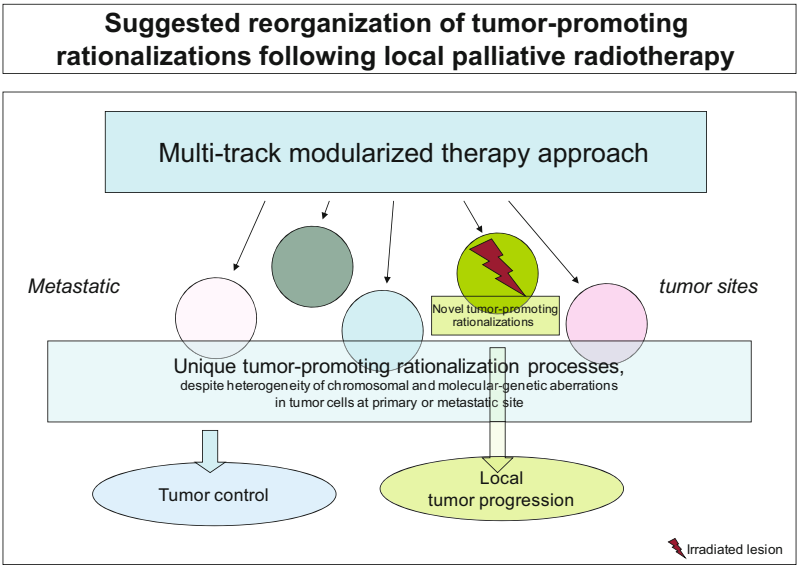


Fig. 2.5 Clinical data indicate that radiotherapy commonly leads to a reorganization of rationalizations constituting tumor-promoting normative notions and consecutive to resistance towards combined modularized tumor therapies

Table 2.8 Combined transcriptional modulation led to an impressive redirection of the tumors' normativity in quite different tumor histologies. Induction of biological memory (more than 10 fold longer times to PSA doubling after discontinuation of study medication compared to base-line PSA doubling time) and induction of continuous complete remissions are pivotal findings

Combined transcriptional modulation:
Redirection of tumor-associated normative functions
(ASH,Blood 2012;**120**:5029; *World J Urol, 2012; ASCO abstract, 2007; 2011)*

Castration-resistant prostate cancer

(pioglitazone and dexamethasone):
• *Anti-osteoblastic effect*
• *Immunregulatory effect*
• *Long-term response (> 4 years)*
• *Biological memory > 1 year (therapy discontinuation)*

Renal clear cell carcinoma

(pioglitazone and interferon-alpha):
• *Anti-inflammatory effect (interferon-alpha!)*
• *Continuous complete remission (histologically confirmed)*
• *Reduction of metastatic potential*

Multiple myeloma

(pioglitazone and dexamethasone):
• *Continuous complete remission in third-line (>1.0 year)*
• *Anti-inflammatory effect*
• *Rapid increase of serum hemoblobin*

Discussion

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, i.e. the different cell compartments, pathways, oncogenes, tumor suppressor genes, etc. Combined modularized therapies (1) help to detect multifaceted, situatively adapted rationalization processes available for ubiquitously occurring tumor-immanent normative notions [2, 7, 8, 15] and (2) corresponding novel tools of biomarkers [5, 7, 9, 22], (3) may uncover novel regulatory systems in tumor biology (e.g., hubs) (Chaps. 16 and 17), (4) pathologies within communication processes (e.g., inconsistencies, disturbances in intersystemic exchange processes) [7, 24], (5) are a basis for studying communicative rules mediating the 'metabolism' of tumor evolution ([24], Chap. 12), and (6) may pave the way for inducing biological memory in metastatic tumors [25, 26] (Table 2.9, Chap. 19).

Induction of long-term tumor response or continuous complete remission in metastatic tumors indicates that tumor-promoting rationalizations at metastatic sites are uniquely constituted within an individual tumor disease and are efficaciously targeted with combined modularized tumor therapies. This way, biomodulatory therapies overcome the major obstacle of 'bottom-up' strategies, namely cytogenetic heterogeneity in tumor cells at primary and metastatic tumor sites (Figs. 2.4, 2.5).

Table 2.9 Evolution-adjusted tumor pathophysiology enables to study novel biomarkers depicting the evolvability of tumors within their 'living world' as well as the therapy-induced redirection and modulation of the tumors' normativity

Novel tool of biomarkers indicating redirection and evolvability of the tumor's normativity

Biomarkers indicating systems' evolvability within the tumor's ‚living world' (‚universal' surrogates)

- ***‚Universal' surrogates*** *for tumor-associated normative notions, e.g. inflammation: C-reactive protein response (in melanoma, renal clear cell carcinoma, multiple myeloma)*
- ***Late-stage biomarkers*** *(e.g. PPARgamma expression in metastatic melanoma)*
- ***Education:*** *Biological memory (epigenetic changes)*

Technologies recording the redirection of the tumors' normativity

- ***Cellular secretome analytics*** *(substantiating rationalizations of tumor-immanent normative notions, i.e. identity and fuction of cellular compartments)*
- ***Molecular imaging*** *of the tumors' normativity*
- ***Histology-based markers:*** *Markers developing with tumor progression (late-stage markers)*
- ***Epigenetic monitoring*** *(25, 26)*

Vice versa, preceding radiation therapy frequently induces intrinsic resistance towards biomodulatory therapy in irradiated tumor lesions. This observation suggests that radiation therapies accomplish heterogeneity of the tumor's growth-promoting rationalization processes as cause for resistance towards combined modularized tumor therapies.

Understanding systems biology as adjustable size ('top-down' technology) may break through the barrier of complex tumor-stroma-interactions in a therapeutically relevant way (Table 2.7): Comparatively high efficacy at moderate toxicity. Structured systems-directed therapies in metastatic cancer may get a source for detecting the topology of tumor-associated complex aggregated action effects accessible for combined modularized therapies (Figs. 2.4, 2.5).

Biomodulatory therapies are tools for uncovering novel modular structures and rationalizations in tumor systems, for probing cellular activation states and for identifying key hubs in both normal and diseased tissues. The concept of protein modularity is central to the field of combined modularized therapies and synthetic biology [7, 27]. With biomodulatory therapies we may design new approaches to disrupt tumor-promoting signaling via remodeling of signaling pathways based on principles derived from modular tumor pathophysiology [22, 28–30].

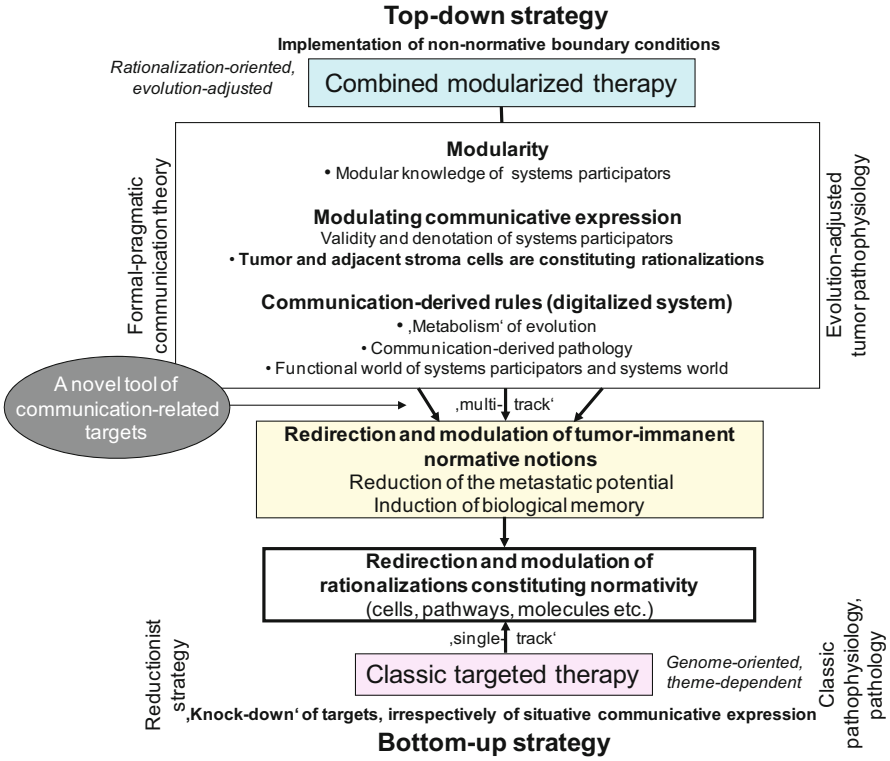


Fig. 2.6 Applied systems biology for the control of metastatic cancer: Shaping and focusing systems' communication by disrupting the holistic thicket with a 'top-down' strategy. Tumors are not any more considered as 'objects', which have to be destroyed with 'single track' or combined 'single track' targeted therapy approaches, but as subjects within a communicative context, which allow to implement multifold novel combined modularized therapies (multi-track approaches). Bottom-up and top-down strategy have in common to redirect and modulate the tumors' normativity as prerequisite for tumor growth control

Observations on the activity profile of combined modularized therapies, i.e. rapid versus delayed response, induction of biological memory, the possibility to achieve response induction via purposive-rational modulation and redirection of tumor-associated normative notions, and the successful application of drug repurposing may not be explained with traditional evolution historical considerations, but facilitate the development of an evolution theory, i.e. the formal-pragmatic communication theory [31, 32].

Specifying 'top-down' approaches necessitates novel pathophysiological considerations, the application of an evolution-adjusted tumor pathophysiology, which focuses on the systematic comprehension of tumor systems objects' communicative expression, their validity and denotation in a distinct evolutionary context (Fig. 2.6).

Evolution-adjusted tumor pathophysiology provides contently and methodologically novel approaches to succeed in personalizing tumor therapy. By targeting the tumors' normativity, genetically based tumor heterogeneity is efficaciously addressed [33]. Uniquely constituted rationalization processes within a distinct tumor disease are a common denominator for successful modular therapeutic access and long-term tumor control.

Evolution-adjusted tumor pathophysiology should be introduced as clinically orientated discipline, equivalent with traditional disciplines, thereby increasing their value and accomplishing ethical demands. A tumor type-specific, systems stage-specific, metastatic site-specific or disease trait-orientated therapy seems to be within grasp.

Acknowledgement This work was greatly facilitated by the use of previously published and publicly accessible research data, also by the systems-theoretical considerations of J Habermas. I would like to thank all colleagues who contributed to the multi-center trials.

References

1. Bundscherer A, Reichle A, Hafner C, Meyer S, Vogt T (2009) Targeting the tumor stroma with peroxisome proliferator activated receptor (PPAR) agonists. Anticancer Agents Med Chem 9(7):816–821. (Review)
2. Hafner C, Reichle A, Vogt T (2005) New indications for established drugs: combined tumor-stroma-targeted cancer therapy with PPARgamma agonists, COX-2 inhibitors, mTOR antagonists and metronomic chemotherapy. Curr Cancer Drug Targets 5(6):393–419. (Review)
3. Gehrmann M, Brunner M, Pfister K, Reichle A, Kremmer E, Multhoff G (2004) Differential up-regulation of cytosolic and membrane-bound heat shock protein 70 in tumor cells by anti-inflammatory drugs. Clin Cancer Res 10(10):3354–3364
4. Gottfried E, Rogenhofer S, Waibel H, Kunz-Schughart LA, Reichle A, Wehrstein M, Peuker A, Peter K, Hartmannsgruber G, Andreesen R, Kreutz M (2011) Pioglitazone modulates tumor cell metabolism and proliferation in multicellular tumor spheroids. Cancer Chemother Pharmacol 67(1):117–126
5. Reichle A, Grassinger J, Bross K, Wilke J, Suedhoff T, Walter B, Wieland WF, Berand A, Andreesen R (2007) C-reactive protein in patients with metastatic clear cell renal carcinoma: an important biomarker for tumor-associated inflammation. Biomark Insights 7(1):87–98
6. Paulitschke V, Gruber S, Hofstätter E, Haudek-Prinz V, Klepeisz P, Schicher N, Jonak C, Petzelbauer P, Pehamberger H, Gerner C, Kunstfeld R (2012) Proteome analysis identified the PPARγ ligand 15d-PGJ2 as a novel drug inhibiting melanoma progression and interfering with tumor-stroma interaction. PLoS One 7(9):e46103
7. Reichle A, Hildebrandt GC (2008) Systems biology: a therapeutic target for tumor therapy. Cancer Microenviron 1(1):159–170
8. Reichle A, Vogelhuber M, Feyerabend S et al (2011) A phase II study of imatinib with pioglitazone, etoricoxib, dexamethasone, and low-dose treosulfan: combined anti-inflammatory, immunomodulatory, and angiostatic treatment in patients (pts) with castration-refractory prostate cancer (CRPC). J Clin Oncol 29(Suppl; abstr 4599)
9. Walter B, Schrettenbrunner I, Vogelhuber M, Grassinger J, Bross K, Wilke J, Suedhoff T, Berand A, Wieland WF, Rogenhofer S, Andreesen R, Reichle A (2012) Pioglitazone, etoricoxib, interferon-α, and metronomic capecitabine for metastatic renal cell carcinoma: final results of a prospective phase II trial. Med Oncol 29(2):799–805

10. Meyer S, Vogt T, Landthaler M, Berand A, Reichle A, Bataille F, Marx AH, Menz A, Hartmann A, Kunz-Schughart LA, Wild PJ (2009) Cyclooxygenase 2 (COX2) and peroxisome proliferator-activated receptor gamma (PPARG) are stage-dependent prognostic markers of malignant melanoma. PPAR Res 2009:848645. (Epub 2009)
11. Reichle A, Vogt T, Coras B, Terheyden P, Neuber K, Trefzer U, Schultz E, Berand A, Bröcker EB, Landthaler M, Andreesen R (2007) Targeted combined anti-inflammatory and angiostatic therapy in advanced melanoma: a randomized phase II trial. Melanoma Res 17(6):360–364
12. Coras B, Hafner C, Reichle A, Hohenleutner U, Szeimies RM, Landthaler M, Vogt T (2004) Antiangiogenic therapy with pioglitazone, rofecoxib, and trofosfamide in a patient with endemic Kaposi sarcoma. Arch Dermatol 140(12):1504–1507
13. Reichle A, Bross K, Vogt T, Bataille F, Wild P, Berand A, Krause SW, Andreesen R (2004) Pioglitazone and rofecoxib combined with angiostatically scheduled trofosfamide in the treatment of far-advanced melanoma and soft tissue sarcoma. Cancer 101(10):2247–2256
14. Vogt T, Hafner C, Bross K, Bataille F, Jauch KW, Berand A, Landthaler M, Andreesen R, Reichle A (2003) Antiangiogenetic therapy with pioglitazone, rofecoxib, and metronomic trofosfamide in patients with advanced malignant vascular tumors. Cancer 98(10):2251–2256
15. Walter B, Rogenhofer S, Vogelhuber M, Berand A, Wieland WF, Andreesen R, Reichle A (2010) Modular therapy approach in metastatic castration-refractory prostate cancer. World J Urol 28(6):745–750
16. Hau P, Kunz-Schughart L, Bogdahn U, Baumgart U, Hirschmann B, Weimann E, Muhleisen H, Ruemmele P, Steinbrecher A, Reichle A (2007) Low-dose chemotherapy in combination with COX-2 inhibitors and PPAR-gamma agonists in recurrent high-grade gliomas—a phase II study. Oncology 73(1–2):21–25
17. Vogt T, Coras B, Hafner C, Landthaler M, Reichle A (2006) Antiangiogenic therapy in metastatic prostate carcinoma complicated by cutaneous lupus erythematodes. Lancet Oncol 7(8):695–697
18. Reichle A, Vogt T, Kunz-Schughart L, Bretschneider T, Bachthaler M, Bross K, Freund S, Andreesen R (2005) Anti-inflammatory and angiostatic therapy in chemorefractory multisystem Langerhans' cell histiocytosis of adults. Br J Haematol 128(5):730–732. (No abstract available)
19. Reichle A**,** Hart C, Grube M, Andreesen R (2012) Anti-Inflammatory, immuno-modulatory and angiostatic treatment as third-line therapy for multiple myeloma (MM)—a combined treatment setting of lenalidomide with pioglitazone, dexamethasone and low-dose treosulfan (phase I/II) blood (ASH Annual Meeting Abstracts) 120**:**5029
20. Paulitschke V, Gruber S, Hofstätter E, Haudek-Prinz V, Klepeisz P, Schicher N, Jonak C, Petzelbauer P, Pehamberger H, Gerner C, Kunstfeld R (2012) Proteome analysis identified the PPARγ ligand 15d-PGJ2 as a novel drug inhibiting melanoma progression and interfering with tumor-stroma interaction. PLoS One 7(9):e46103
21. Emmenegger U et al (2010) The biomodulatory capacities of low-dose metronomic chemotherapy: complex modulation of the tumor microenvironment. In: From molecular to modular tumor therapy: the tumor microenvironment, vol 3, part 3. Springer, Berlin, pp 243–262. doi:10.1007/978–90-481–9531-2_11
22. Meyer S, Vogt T, Landthaler M, Bataille F, Reichle A, Marx A et al (2010) Cyclooxygenase2 (COX2) and peroxisome proliferator-activated receptor gamma (PPARG) are stage-dependent prognostic markers of malignant melanoma. In: Reichle A (ed) From molecular to modular tumor therapy: the tumor microenvironment, vol 3, part 6. Springer, Berlin, pp 443–65. doi:10.1007/978–90-481–9531-2_22
23. Reinhold SW, Reichle A, Leiminger S, Bergler T, Hoffmann U, Krüger B, Banas B, Krämer BK (2011) Renal function during rofecoxib therapy in patients with metastatic cancer: retrospective analysis of a prospective phase II trial. BMC Res Notes 4:2–6
24. Reichle A, Hildebrandt GC (2010) The comparative uncovering of tumor systems biology by modularly targeting tumor-associated inflammation. In: From molecular to modular tumor therapy: the tumor microenvironment, vol 3, part 4. Springer, Berlin, pp 287–303. doi:10.1007/978–90-481–9531-2_13

25. Grønbæk K, Müller-Tidow C, Perini G, Lehmann S, Bach Treppendahl M, Mills K, Plass C, Schlegelberger B (2012) European genomics and epigenomics study on MDS and AML (EuGESMA), COST action BM0801. A critical appraisal of tools available for monitoring epigenetic changes in clinical samples from patients with myeloid malignancies. Haematologica 97(9):1380–1388
26. Kanwal R, Gupta S (2012) Epigenetic modifications in cancer. Clin Genet 81(4):303–311
27. Nash PD (2012) Why modules matter. FEBS Lett 586(17):2572–2574
28. Haura EB (2012) From modules to medicine: how modular domains and their associated networks can enable personalized medicine. FEBS Lett 586(17):2580–2585
29. Pan CQ, Low BC (2012) Functional plasticity of the BNIP-2 and Cdc42GAP Homology (BCH) domain in cell signaling and cell dynamics. FEBS Lett 586(17):2674–2691
30. Joshua A Jadwin JA, Ogiue-Ikeda M, Machida K (2012) The application of modular protein domains in proteomics. FEBS Lett 586(17):2586–2596
31. Reichle A, Hildebrandt GC (2009) Principles of modular tumor therapy. Cancer Microenviron 2(Suppl 1):227–237
32. Reichle A (ed) (2010) From molecular to modular tumor therapy: the tumor microenvironment, vol 3. doi:10.1007/978–90-481–9531-2
33. Gerlinger M, Rowan AJ, Horswell S, Larkin J, Endesfelder D et al (2012) Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 366(10):883–892