Chapter 10
The Tumor's Normativity: Normative Structures, Action Norms and Decision Maxims as Therapeutic Targets for Tumor Therapy

Albrecht Reichle and Joachim Hahn

Abstract Are normative notions, i.e., normative structures (morphology, and topology), action norms (including the hallmarks of cancer), and decision maxims (hubs, nodes) physically rationalized, functionally established, and even protected? The inseparable relation between rationalization processes and normative notions may be shown at three observational levels. (1) For many reasons, normative notions do not constitute a posteriori classifying phrases or dummies that hide a broad variety of arbitrary tumor-associated phenomena. On the contrary, normative notions are a source of the 'metabolism' of evolution, supplied by the substance of all rationalization processes mediating normative structures, action norms, and decision maxims. (2) Furthermore, the catalytic role of normative notions in composing rationalization processes of the 'metabolism' of evolution can be systematically highlighted from historic aspects and from a therapeutic point of view. (3) Finally, the origin of rationalization processes deriving from normative notions explains the context-disrupting explosive nature of a concrete 'utopia' realized in a normative notion. This condition turns on the general distortion of rationalization processes in tumors (inconsistencies, deformations, and Achilles' heels) as well as on their radical substance (corrupt rationalizations), which is best outlined by its observable robustness towards external (therapeutic) disturbances. The study of normative notions and respective rationalizations in tumor systems including their systematic classification needs to be institutionalized to constitute evolution-adjusted tumor pathophysiology as the novel language of tumor biology and to facilitate biomodulatory therapy approaches.

Keywords Normative notions · Rationalization · Tumor pathophysiology · Convergent evolution · Biomodulatory therapy · Acute myelocytic leukemia

A. Reichle (✉) · J. Hahn
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_10,

Introduction

The present article aims at further investigating the question whether normative notions, i.e., normative structures (morphology and topology), action norms (inclusively the hallmarks of cancer, i.e., sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, reprogramming of energy metabolism, evading immune destruction as well as genome instability and tumor-associated inflammation), and decision maxims (hubs and nodes), as purposive action profiles of a tumor compartment are arbitrarily selected for better comprehension of the validity and denotation of tumor systems objects, i.e., pathways, cells, gene expression profiles, transcription factors, cell interactions, etc. The second question is whether normative notions become—to the contrary—physically rationalized, functionally established, and even protected because of their fail-safe maintenance properties [1–4]. Thus, normative notions would be also constitutive for the 'metabolism' of evolution in tumors.

Considering the multifold possibilities (redundancy) of how cells or cell communities constitute rationalizations for the fail-safe function as well as the frequent context-dependent multifunctionality of tumor systems objects—exemplified by NF-κB and p53—, we may become confused about the 'true' assessment of the communicative expression of tumor systems objects or their denotation within established rationalization processes [5, 6].

In contrast to the assumption of an retrospectively ensued contentual loading of the term 'rationalization', we would like to show that a tight conceptual and scientifically verifiable coherence has existed between the two concepts 'rationalization' and 'normative notions' from the very beginning, even though only implied as 'tumor-associated angiogenesis' or 'tumor-associated inflammation' (the hallmarks of cancer), etc. Consecutively, the evolution-historic way, i.e., how rationalizations are constituted in molecular detail, reaches therapeutic relevance. Likewise, the pure molecular identity of a potential therapeutic target dwindles in importance because its situative communicative expression has to be added for guiding therapeutic decisions and personalizing systemic tumor therapies [7].

The evolutionary-driven constitution of the normative substance of rationalization processes as well as the cellular recourse on distinct and—within an evolutionary context—restricted tools of rationalizations for the fail-safe maintaining of normative notions draws on communicative competition, even if 'corrupt' rationalizations develop, as in the case of tumors. On the basis of non-random multifacetedly acquired molecular-genetic aberrations, tumors represent a very good example and model to investigate the diversity of 'individual' rationalizations, particularly in tumor entities such as acute leukemia [8].

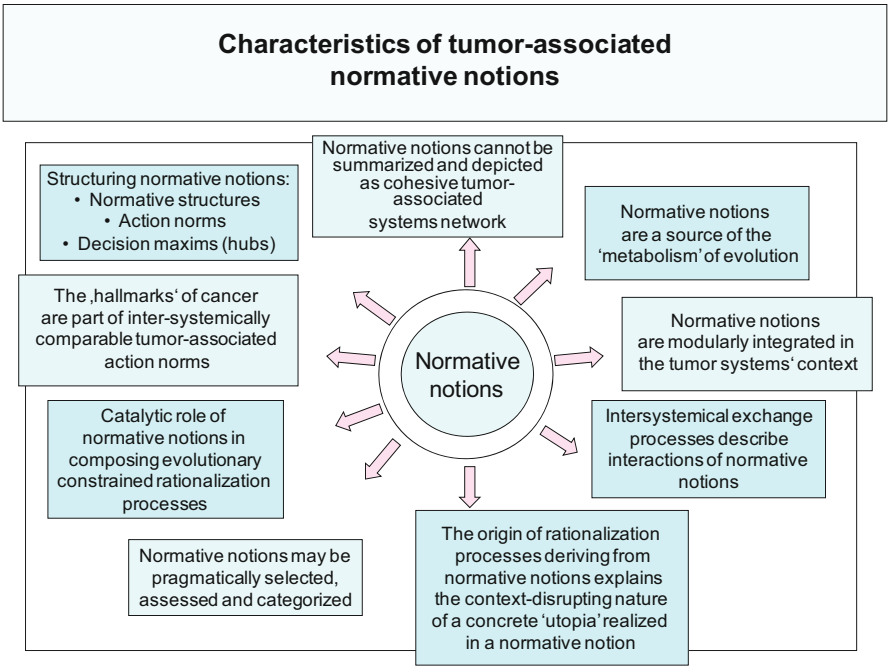

Fig. 10.1 Features of tumor-immanent normative notions

Method

The inseparable relation between rationalization processes, which are supposed to organize and to ensure the physical expansion and maintenance of normative notions, and normative notions may be shown at three observation levels, (1) genetic code—rationalization—normative notion, (2) biomodulatory therapies—rationalizations—normative notion, and (3) communication-derived pathophysiology of rationalizations of normative notions (Fig. 10.1).

1. For many reasons (i.e., context-dependent validity and denotation of tumor systems objects; convergent evolution, that means multiple rationalizations for one dominant normative notion; and robustness of rationalizations), normative notions do not constitute a posteriori classifying phrases or dummies that hide a broad variety of arbitrary tumor-associated phenomena. On the contrary, normative notions are a source of the 'metabolism' of evolution, supplied by the substance of all rationalization processes mediating normative structures, action norms, and decision maxims.
2. Furthermore, the catalytic role of normative notions in composing rationalization processes of the 'metabolism' of evolution and rationalization can be systematically highlighted from historic aspects and from a therapeutic point of view.

3. Finally, the origin of rationalization processes deriving from normative notions explains the context-disrupting explosive nature of a concrete 'utopia' realized in a normative notion. This condition turns in a scientifically accessible way on the general distortion of rationalization processes in tumors (inconsistencies, deformations, Achilles' heels) as well as on their radical substance (corrupt rationalizations), which is best outlined by its observable robustness towards (therapeutic) disturbances from outside.

Results and Discussion

Ad 1) Because of their abstract universality, the normative structures, action norms, and decision maxims of tumors require concretization in each separate case, i.e., description of cellular, biochemical, and systems levels and specification of the stage-dependent physical constitution in an evolutionary context.

Thereby, multifaceted acquired digitalized structures, which are anchored in the genetic code and constitute the frame for distinct normative notions via rationalizations, may attain multifaceted starting points to establish unique normative notions[8]: Convergent evolution [9] may be even highlighted in acute leukemia. The already anamnestically obvious, rapid onset of leukemia-associated symptoms——induced by bone marrow insufficiency—is marked by a very broad variety of single or cumulatively acquired molecular-genetic aberrations. As the different types of acute leukemia share a dominant normative notion, rapidly displacing growth, the notion achieves facticity: Rapid leukemia evolution may be realized by the 'metabolism' of evolution via multifaceted and differentially established rationalizations. Kvinlaug et al. causatively described the occurrence of 'disparate oncogenes' [8]: Differential functions may be attributed to oncogenes dependent on the leukemia-specific concert of aberrations. Beyond the context-dependent acquisition of differential functions of oncogenes or driver mutations, their predictive value may change dependent on the additional clinical background, which again is founded in the concert of molecular-genetic aberrations [10].

The redemption of a unique normative notion from scientifically and profoundly assessed multifaceted genetic starting points including frequently occurring recurrent genetic aberrations outlines the varying validity and denotation of single aberrations against the background of an evolutionary specified genetic context. Multifaceted aberrant genomes constitute a broad diversity of rationalizations for maintaining the dominant normative notion, according to which a whole group of diseases, namely 'acute' leukemia, is clinically classified [11].

Now, differential rationalizations constituting a unique phenotype achieve an equivalent classifying substance and could present as decisive guides for 'rationalization-targeted' (personalized) therapies in future. Furthermore, tumor-specific and stage-specific rationalizations with entirely unforeseen validity and denotation of underlying oncogene-addicted structures, driver mutations or generally therapeutic targets are the major reason for the limited practice of so-called targeted therapies in unknown and novel evolutionary systems stages [8, 12]. The

Table 10.1 Top-down and bottom-up strategies use quite different targets for redirecting and modulating the tumor's normativity

Therapeutic top-down versus bottom-up strategy	
• **Evolution-adjusted approach**	• **Theme-dependent approach**
Targets:	**Targets:**
• Tumor-immanent normative notions (implementation of non-normative boundary conditions)	• Systems participators as ‚artifacts', irrespectively of their validity and denotation
• Rationalization processes	• Cell-specific targets
• Systems participator's validity and denotation	• Oncogenic targets
• Ubiquitously in tumor and stroma cells accessible targets	• Pathways
• Tumor and stroma cells are equally targeted	• Malignant cell populations, rarely stroma cells

frequently weak efficacy of classic targeted therapies empirically underlines the heterogeneity of rationalizations, particularly in the molecular-genetically highly heterogeneous types of acute leukemia. The novel classifying principle, i.e., the systematic comprehension of rationalizations at genetic and protein level etc., will lead to evolution-adjusted tumor pathophysiology (Table 10.1).

Accordingly, normative notions subsume more subjacent differences, such as multifaceted rationalization processes. The function of a communicatively determined compromise, which normative notions accomplish in the course of the differentiation and expansion of rationalization processes, may not explain their occurrence as a specified rationalization concept in tumors. Experimental data on context-dependent functionality—particularly of transcription factors—and clinical data obtained through biomodulatory therapy approaches show that modified evolutionary contexts only communicatively address the aspects that are implicitly inscribed in rationalization processes, namely normative structures, action norms, and decision maxims [13–16].

Correspondingly, cells refer back to repair mechanisms or mobilize alternative rationalization processes from an accessible tool to maintain normative notions (robustness) if normative structures are exposed to unexpected perturbations [17]. Hence, detection of violated normative notions and respective repair mechanisms have the function of uncovering communicative rules as well as inconsistencies, deformations, and Achilles' heels of expanding rationalizations during tumor evolution.

From the capacity to focus on the protection of normative notions, the importance may be delineated, which robustness [18–20] has achieved for the fail-safe function of rationalization processes. The stronger robustness permeates the whole system of cellular rationalizations, the more frequent its interference with the vertical relation between single cells. Just in the case of tumor development, collisions accumulate (implementation of molecular-genetic abnormalities, 'stress'), necessitating intercellular communicative assessment between competitive rationalization claims according to communication-derived rules. In such decisive 'hard cases', decisions are only possible by a recourse on the violation of a valid and priority-claiming normative notion (which could also be therapeutically supported for prevention). In the case of tumor initiation, an overthrown normative notion may be uncovered within a 'physiologic' cell compartment accompanied with a corrupt rationalization.

The 'hard case' may be simulated by the experimental implementation of non-normative boundary conditions, e.g., cellular 'stress' in prostate cancer cell lines, which alters the denotation of the androgen receptor. The receptor then physically participates in establishing a recurrent chromosomal translocation, TMPRSS2:ERG and TMPRSS2:ETV1 ('corrupt' rationalization following androgen treatment and genotoxic stress): A distinct, externally implemented rationalization leads to specific chromosomal aberrations, indicating that rationalizations are principally in bidirectional communicative exchange with the digitalized system of the genome [21]. Rationalizations are—on the basis of normative notions and the 'metabolism' of evolution—the digitalized counterpart of the genetic code and may contribute to decipher the genome-centric 'world'.

After having systematically observed tumor development on the basis of increasing lifetime expectation for many decades and the introduction of steeply growing numbers of technologies and (biomodulatory) therapies for studying cancer, we now realize the benchmarks of tumor development: Normative notions, which outreach the traditionally noted hallmarks of cancer by far, are the framework by which the universal substance of the 'metabolism' of evolution is imported into novel rationalization processes.

The idea of normative notions is the conceptual hinge that merges the 'metabolism' of evolution in every cellular structure and function with respective physically comprehensive and directly scientifically accessible rationalization processes. This mergence occurs in such a way that a distinct cellular organization originates from the interplay at a circumscriptive and compliantly evolutionary stage (cellular 'living' world), which is based on the robustness of different rationalization processes. As the 'metabolism' of evolution may be redeemed in specified rationalizations, the expansion of rationalizations shows a Janus face, which is simultaneously directed at the 'metabolism' of evolution and at the communication-derived norms (rules) for constituting rationalizations [22].

Ad 2) To date, normative structures (for instance, molecular-genetic aberrations in tumor and stroma cells) and action norms, such as the hallmarks of cancer, constitute a realistic utopia insofar as they do not make us believe any longer that tumor cells are a contextless driving force during their evolution [23]. But simultaneously, we only hesitantly dare to attribute concrete validity and denotation to individual and

multifacetedly differentiated tumor cell components. Anyhow, normative structures, i.e., angiogenesis, inflammation etc., are acknowledged 'per se' as indispensable for tumor development [3, 24].

The following tasks are crucial for extending the instruments for designing personalized therapy approaches: to estimate the situate validity and denotation of normative notions in the tumor compartment, to get information on the communicatively guided competition of various normative structures in the tumor, to identify the particular cellular driving sources, and to analyze how normative notions are physically and functionally rationalized in a distinct evolutionary context. This way, rationalization processes may be categorized beyond the traditional classifying principles, i.e., disease traits and histopathology, which redraws the attention to tumor pathophysiology. Tumor pathophysiology needs to be reconsidered and may have to be re-established as evolution-adjusted, clinical, and particularly personalized tumor pathophysiology [25].

Biomodulatory therapies are directed towards robustness of rationalization processes by redeeming novel validity and denotations of systems objects in the context of a tumor's evolutionary confined 'living' world, i.e., its holistic communicative world [26]. Vice versa, biomodulatory therapies may give decisive clues how normative notions are rationalized in a distinct evolutionary context, as exemplified by modularly targeting tumor-associated inflammation [27].

The proper functioning of biomodulatory therapies in metastatic cancer underlines that regulatory active, multi-targeted therapy approaches, which primarily focus on non-oncogene addicted structures and functions, may exhaust the communicative capacity of a tumor's 'living' world [14, 16]. Thereby, normative notions, which are basically supported by 'oncogene'-addicted structures and functions become redirected and placed. In acute myelocytic leukemia, first biomodulatory therapy approaches with a nuclear receptor agonist, i.e., all-trans-retinoic acid, have shown significantly improved overall survival rates in cytogenetically defined subgroups, besides the classic application in promyelocytic leukemia [28]. All these therapy-derived observations indicate that the normative notions of tumors are therapeutically placeable via communication-derived rules grounded in a tumor's 'living' world: Normative notions, which are frequently accessible as disease traits—as in the case of 'acute' leukemia—, are available for therapeutic modification by implementing rationalization-specific and non-normative boundary conditions, i.e., biomodulatory therapies (transcriptional modulators, metronomic low-dose chemotherapy, etc.) [14]. Because of the established and therapeutically relevant altered communicative prepositions during biomodulation, the term 'oncogene' must be relativized, because only the therapy-naive tumor-associated communicative context refers to the denotation as 'oncogene', which again may be specified in the context of multiple additional molecular-genetic aberrations ('disparate' oncogenes).

Ad 3) Reductionist-oriented targeted therapies provoke tension in the current therapeutic scene: Apart from some exceptions, therapeutic results obtained by reductionist approaches disclose more and more frequently a gap between the perceived (preclinical) norms and expectations—stated by reductionist theories on oncogene-addicted targets or driver mutations—and current, rarely sweeping therapy results,

which are often taken from very small patient populations [29–33]. Reductionist knowledge draws on uniquely defined communicative circumstances, which are self-evidently assigned to novel evolutionary confined systems stages, as is the case in the therapy of acute leukemia. The strategy to target oncogene-addicted structures and driver mutations is commonly linked to the perception of personalized tumor therapy.

The interruption of a rationalization process at any optional biochemical level (traditional targeted therapy), necessitates the tumor's living world to react with alternative rationalizations. In the situative communicative expression of a target lies the rub, as seemingly unexpected 'effects' and 'side effects' may occur. Reproducibility of side effects, and side effects dependent on the treated histological tumor type, as outlined for sorafenib, a tyrosine kinase inhibitor, and its differential activity in acute myelocytic leukemia, renal clear cell carcinoma and hepatocellular carcinoma [12, 34, 35], again underline that rationalizations are highly specific.

However, the novel practice of creating applied systems biological therapy approaches brings on a completely new problem: Biomodulatory therapies also claim universal validity. They aim at targeting the weak points in the execution of rationalization processes or at redirecting a tumor's normative notions to achieve the attenuation of tumor growth. Basis for the therapy design is the analytic and empiric comprehension of tumor-associated rationalizations, which equally encompass both the digitalized genome-centric 'world' and the modularly structured cellular 'world' [26, 27, 36, 37]: The tumor's rationalizations represent an independent counterpart to the tumor's genome with its acquired aberrations.

For establishing evolution-adjusted tumor pathophysiology, each norm, the substance of a systems object (i.e., its background knowledge), is scrutinized with regard to its communicative context, which attributes notable validity and denotation to systems objects in a distinct evolutionary systems stage [27]. Does a novel evolutionary context attribute identical validity and denotation to a systems object as uncovered for the respective systems object in the evolutionary context studied originally? Is the respective systems object part of a novel rationalization process, constituting a distinct normative notion [12]? Multifold experimental data highlight NF-κB as a colorful 'matchmaker', when inflammation meets cancer [38].

Normative notions may be studied starting with the comprehension of the tool of possible rationalization processes (redundancy, robustness), for example, by describing which cell compartments primarily contribute to tumor-associated inflammation, angiogenesis, immune response etc., and which communication lines are activated with regard to communicative expression. Furthermore, normative notions may be studied by recording the secretome of cellular compartments of the tumor in patient serum, which is indicative for the presence of distinct normative notions, or by monitoring changes derived from molecular imaging, which may give indications for the therapeutic redirection of normative notions [27, 39–41].

Table 10.2 Rationalizations of tumor-immanent normative notions represent the non-genomic counterpart of the tumor genome and have to be systematized in the same way as genomic structures and functions

Rationalizations:
The non-genomic counterpart of the tumor genome

Tumor genome	Tumor-associated rationalizations
Coding, non-coding gene sequences, transcription process	Rationalization processes constitute between the poles of systems world and functional world of systems participators
Digitalized system	Digitalized, endogenously and therapeutically redeemable system (does not exclude analogously working functions)
Number of genes circumscript (whole genome analysis)	Number of therapy-relevant rationalizations discursively and pragmatically assessable
Functional genomics	Intersystemically comparable, interphases between rationalizations
Intratumoral genetic heterogeneity	Rationalizations can be maintained within a tumor disease of a patient, presumably via hubs
Targeting of moleculargenetic aberrations: ‚Bottom-up' strategies	Targeting of rationalizations: ‚Top-down' strategies

Conclusion

Normative notions are pragmatically and discursively selected. The study of normative notions (Fig. 10.1) and respective rationalizations in tumor systems including their systematic classification needs to be institutionalized to constitute evolution-adjusted tumor pathophysiology as the novel language of tumor biology and to facilitate novel biomodulatory therapy approaches, i.e., cellular therapies in situ (Table 10.2).

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

Glossary

Normative notions
Normative notions comprise defaults in biologic systems, which are realized by evolutionarily compliant rationalizations. For their formal description the discrimination between normative structures (morphology, topology), action norms (e.g., hallmarks of cancer) and decision maxims (nodes, hubs) is useful. The idea of normative notions is the conceptual hinge that merges the 'metabolism' of evolution in every cellular structure and function with respective physically comprehensive and directly scientifically accessible rationalization processes. Normative notions, which outreach the traditionally noted hallmarks of cancer by far, are the framework by which the universal substance of the 'metabolism' of evolution is imported into novel rationalization processes.

Rationalization
Rationalizations describe how normative notions, i.e., normative structures, action norms and decision maxims are differentially and physically established as well as functionally organized [7]. Rationalizations equally encompass both the digitalized genome-centric 'world' and the modularly structured cellular 'world' [26, 27, 36].

Modularity
In the present context, modularity is a formal pragmatic communicative systems concept, describing the degree and specificity to which systems objects (cells, pathways, proteins etc.) may be communicatively separated in a virtual continuum and recombined and rededicated to alter the validity and denotation of communication processes in the tumor.

Tumor's living world
The living world comprises the tumor's holistic communication processes, which we rely on in every therapy. With experimental or therapeutic experiences (modular therapies) the tumor's living world may be separated into categories of knowledge, for example, into modular systems. Specific conditions of compliance, for redeeming validity constitute relations between communication technique (specified biomodulatory therapy approaches) and distinct tumor-associated systems stages [26].

Background knowledge
The communicative substance of a systems object is dependent on the communicative presuppositions, which determine the system's object validity and denotation within an evolutionary compliant systems stage. Background knowledge constitutes the validity of informative intercellular processes, which is the prerequisite for therapeutic success. Background knowledge about the tumor's living world is subjected to other conditions of scientific comprehension: Intentional ways fail to describe risk-absorbing knowledge, in which context-dependent knowledge about commonly administered reductionist therapy approaches is rooted. After this second objectifying step (physicians as operators of tumor systems), the network of the holistic

communicative activities turns out to be the medium through which the tumor's living world is mirrored and generated in rationalizations [26].

'Metabolism' of Evolution

Generally, communicatively linked biological systems are interweaving the nude identity of their systems' objects, or the arrangement of compartmentalized knowledge (on the observer site) with situative biological stages, or with communicative arrangements of systems' objects validity and denotation (on the participator site) by allowing implementation of internally or externally derived modular knowledge according to rules, which are present in modularly arranged and rationalized systems' textures, equitable with the metabolism of evolutionary systems, and which purport the frame for evolutionary multiplicity [22]. As the 'metabolism' of evolution may be redeemed in specified rationalizations, the expansion of rationalizations shows a Janus face, which is simultaneously directed at the 'metabolism' of evolution and at the communication-derived norms (rules) for constituting rationalizations.

References

1. Puglisi R, Maccari I, Pipolo S, Conrad M, Mangia F, Boitani C (2011) The nuclear form of Glutathione Peroxidase 4 is associated with sperm nuclear matrix and is required for proper paternal chromatin decondensation at fertilization. J Cell Physiol. doi: 10.1002/jcp.22857
2. Galon J, Costes A, Sanchez-Cabo F et al (2006) Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 313:1960–1964
3. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144(5):646–674 (Review)
4. Kar G, Gursoy A, Keskin O (2009) Human cancer protein-protein interaction network: a structural perspective. PLoS Comput Biol 5(12):e1000601
5. Ben-Neriah Y, Karin M (2011) Inflammation meets cancer, with NF-κB as the matchmaker. Nat Immunol 12(8):715–723
6. Menendez D, Inga A, Resnick MA (2009) The expanding universe of p53 targets. Nat Rev Cancer 9(10):724–737
7. Reichle A (2009) Tumor systems need to be rendered usable for a new action-theoretical abstraction: the starting point for novel therapeutic options. Curr Cancer Ther Rev 5(10):232–242
8. Kvinlaug BT, Chan WI, Bullinger L, Ramaswami M, Sears C, Foster D, Lazic SE, Okabe R, Benner A, Lee BH, De Silva I, Valk PJ, Delwel R, Armstrong SA, Döhner H, Gilliland DG, Huntly BJ (2011) Common and overlapping oncogenic pathways contribute to the evolution of acute myeloid leukemias. Cancer Res 71(12):4117–4129
9. Gatenby RA, Gillies RJ, Brown JS (2011) Of cancer and cave fish. Nat Rev Cancer 11(4):237–238
10. Pfirrmann M, Ehninger G, Thiede C, Bornhäuser M, Kramer M, Röllig C, Hasford J, Schaich M (2011) For the study alliance leukaemia (SAL). Prediction of post-remission survival in acute myeloid leukaemia: a post-hoc analysis of the AML96 trial. Lancet Oncol (Epub ahead of print)
11. Marcucci G, Haferlach T, Döhner H (2011) Molecular genetics of adult acute myeloid leukemia: prognostic and therapeutic implications. J Clin Oncol 29(5):475–486 (Epub 2011 Jan 10. Review. Erratum in: J Clin Oncol 29(13):1798)
12. Reichle A (2011) Biomodulatorische Therapiemöglichkeiten beim Nierenzellkarzinom. J Onkologie 6:21–24

13. Heinz S, Glass CK (2011) Roles of lineage-determining transcription factors in establishing open chromatin: Lessons from high-throughput studies. Curr Top Microbiol Immunol (Epub ahead of print)
14. Reichle A, Hildebrandt GC (2008) Systems biology: a therapeutic target for tumor therapy. Cancer Microenviron 1(1):159–170
15. Reichle A, Vogt T, Coras B, Terheyden P, Neuber K, Trefzer U, Schultz E, Berand A, Brocker EB, Landthaler M, Andreesen R (2007) Targeted combined anti-inflammatory and angiostatic therapy in advanced melanoma: a randomized phase II trial. Melanoma Res 17:360–364. doi: 10.1097/CMR.0b013e3282f1d2c8
16. Reichle A, Vogelhuber M, Feyerabend S, Suedhoff T, Schulze M, Hubner J, Oberneder R, Baier M, Ruebel A, Birkholz K, Bakhshandeh-Bath A, Andreesen R (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
17. Pahler JC, Tazzyman S, Erez N et al (2008) Plasticity in tumor promoting inflammation: impairment of macrophage recruitment evokes a compensatory neutrophil response. Neoplasia 10:329–340
18. Lenz G (2012) Endogenous anticancer mechanisms (EACMs). Front Biosci (Schol Ed) 4:1017–1030
19. Kitano H (2003) Cancer robustness: tumour tactics. Nature 426(6963):125 (No abstract available)
20. Stelling J, Sauer U, Szallasi Z, Doyle FJ, III, Doyle J (2004) Robustness of cellular functions. Cell 118:675–685
21. Lin C, Yang L, Tanasa B et al (2009) Nuclear receptor-induced chromosomal proximity and DNA breaks underlie specific translocations in cancer. Cell 11(139):1069–1083
22. Reichle A, Hildebrandt GC (2010) Searching for the 'metabolism' of evolution. In: From molecular to modular tumor therapy: the tumor microenvironment, vol 3, part 4. Springer, pp 305–309. doi:10.1007/978-90-481-9531-2_14
23. Raaijmakers MH, Mukherjee S, Guo S et al (2010) Bone progenitor dysfunction induces myelo-dysplasia and secondary leukaemia. Nature 21 (Epub ahead of print)
24. Witz IP (2008) Tumor-microenvironment interactions: dangerous liaisons. Adv Cancer Res 100:203–229. doi: 10.1016/S0065-230X(08)00007-9
25. Reichle A (2010) Bridging theory and therapeutic practice: from generalized disease models to particular patients. In: From molecular to modular tumor therapy: the tumor microenvironment, vol 3, part 1. Springer, pp 3–7. doi: 10.1007/978-90-481-9531-2_1
26. Reichle A, Hildebrandt GC (2009) Principles of modular tumor therapy. Cancer Microenviron 2(Suppl 1):227–237
27. 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, pp 287–303. doi:10.1007/978-90-481-9531-2_13
28. Schlenk RF, Fröhling S, Hartmann F, Fischer JT, Glasmacher A, del Valle F, Grimminger W, Götze K, Waterhouse C, Schoch R, Pralle H, Mergenthaler HG, Hensel M, Koller E, Kirchen H, Preiss J, Salwender H, Biedermann HG, Kremers S, Griesinger F, Benner A, Addamo B, Döhner K, Haas R, Döhner H (2004) AML study group Ulm. Phase III study of all-trans retinoic acid in previously untreated patients 61 years or older with acute myeloid leukemia. Leukemia 18(11):1798–1803
29. Soria JC, Mok TS, Cappuzzo F, Jänne PA (2011) EGFR-mutated oncogene-addicted non-small cell lung cancer: Current trends and future prospects. Cancer Treat Rev (Epub ahead of print)
30. Pao W, Girard N (2011) New driver mutations in non-small-cell lung cancer. Lancet Oncol 12(2):175–180 (Review)
31. Choi PS, van Riggelen J, Gentles AJ, Bachireddy P, Rakhra K, Adam SJ, Plevritis SK, Felsher DW (2011) Lymphomas that recur after MYC suppression continue to exhibit oncogene addiction. Proc Natl Acad Sci U S. A 108(42):17432–17437

32. Corbin AS, Agarwal A, Loriaux M, Cortes J, Deininger MW, Druker BJ (2011) Human chronic myeloid leukemia stem cells are insensitive to imatinib despite inhibition of BCR-ABL activity. J Clin Invest 121(1):396–409 (Erratum in: J Clin Invest 121(3):1222)
33. Wassmann B, Pfeifer H, Goekbuget N, Beelen DW, Beck J, Stelljes M, Bornhäuser M, Reichle A, Perz J, Haas R, Ganser A, Schmid M, Kanz L, Lenz G, Kaufmann M, Binckebanck A, Brück P, Reutzel R, Gschaidmeier H, Schwartz S, Hoelzer D, Ottmann OG (2006) Alternating versus concurrent schedules of imatinib and chemotherapy as front-line therapy for Philadelphia positive acute lymphoblastic leukemia (Ph + ALL). Blood 108(5):1469–1477
34. Almhanna K, Philip PA (2009) Safety and efficacy of sorafenib in the treatment of hepatocellular carcinoma. Onco Targets Ther 2:261–267
35. Kane RC, Farrell AT, Saber H, Tang S, Williams G, Jee JM, Liang C, Booth B, Chidambaram N, Morse D, Sridhara R, Garvey P, Justice R, Pazdur R (2006) Sorafenib for the treatment of advanced renal cell carcinoma. Clin Cancer Res 12(24):7271–7278
36. Heng HH, Bremer SW, Stevens JB, Ye KJ, Liu G, Ye CJ (2009) Genetic and epigenetic heterogeneity in cancer: a genome-centric perspective. J Cell Physiol 220(3):538–547 (Review)
37. Yeung WWS, Ho MKC, Wong YH (2010) Functional impacts of signal integration: regulation of inflammation-related transcription factors by heterotrimeric G proteins. In: From molecular to modular tumor therapy: the tumor microenvironment, vol 3, part 3. Springer, pp 161–189. doi: 10.1007/978-90-481-9531-2_9
38. Ben-Neriah Y, Karin M (2011) Inflammation meets cancer, with NF-κB as the matchmaker. Nat Immunol 12(8):715–723
39. Pitteri SJ, Kelly-Spratt KS, Gurley KE, Kennedy J, Buson TB, Chin A, Wang H, Zhang Q, Wong CH, Chodosh LA, Nelson PS, Hanash SM, Kemp CJ (2011) Tumor microenvironment-derived proteins dominate the plasma proteome response during breast cancer induction and progression. Cancer Res 71(15):5090–5100
40. Paulitschke V et al (2010) Secretome proteomics, a novel tool for Biomarkers discovery and for guiding biomodulatory therapy approaches. In: From molecular to modular tumor therapy: the tumor microenvironment, vol 3, part 6. Springer, pp 405–431.doi: 10.1007/978-90-481-9531-2_21
41. Kiessling F, Lederle W (2010) Early detection of systems response: Molecular and functional imaging of angiogenesis. In: Reichle A (ed) From molecular to modular tumor therapy: the tumor microenvironment, vol 3, part 6. Springer, pp 385–403. doi:10.1007/978-90-481-9531-2_20