Chapter 12
Evolution Theory: Its Practical Relevance for Understanding Tumor Development and Specifying Tumor Therapy

A. Reichle and G. C. Hildebrandt

Abstract At that time the introduction of a cancer evolution concept, has failed to revolutionize cancer research. Models of rational reconstruction within an **evolution historical frame** can be suggested, if an innovative achievement may be denoted for a complex 'learning process'. Because such models admit a clear normative reference and action-theoretical interpretation; they may be used for narrative presentations. Three main factors emerged as starting point for **evolution theoretical considerations**, an unmet medical need (systemically pretreated patients with metastatic tumors), a hypothesis-driven vision (the formal pragmatic communication theory) and technological advances to pursue that vision (biomodulatory therapy approaches, clinical proteomics, epigenetics and molecular imaging techniques). An evolution theory allows for virtualizing the engagement to get experiences and decisions (pragmatic virtualization of communication acts) via implementation of non-normative boundary conditions (for example, biomodulatory therapies). The feasibility to virtualize the engagement to get situate experiences about tumor systems and decisions to tailor biomodulatory therapies (communication-derived tumor pathophysiology), the availability of an evolutionarily adapted modeling of cancer (cellular therapy in situ by adaptive therapies) will continue to increase our understanding of tumor pathophysiology and may contribute to an evolution-oriented design of systems biological strategies to diagnose and clinically manage tumor diseases on a novel personalized level. Basic science is getting directly involved in the reconstructive process, even though an approach has been established directed from bedside to bench aimed at implementing clinical practical care (adaptive trial designs) as scientific object in patient care.

A. Reichle (✉)
Department of Hematology and Oncology, University Hospital Regensburg,
93042 Regensburg, Germany
e-mail: albrecht.reichle@klinik.uni-regensburg.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_12, © Springer Science+Business Media Dordrecht 2013

Introduction

A clearer understanding of evolutionary processes involved in the development of tumor growth and metastasis is essential for improving today's patients' prognosis by appropriate cancer treatment, for the efficacious implementation of cancer screening programs and for a better understanding of underlying tumor biology, particularly tumor systems biology. Experimental work suggests that a more comprehensive non-linear interpretation of gene-environment-interactions with integration of communication rules is needed [1].

Central questions may be at least partially answered by an evolution theory of tumors:

- Why are we trying so hard to identify 'universal' patterns of genetic alterations in cancer tissues, although we may identify restricted patterns of normative systems structures in tumors, i.e., rapid proliferation (acute myelocytic leukemia (AML)), dysplasia (myelodysplastic syndrome (MDS)) or apoptosis resistance (chronic myelocytic or lymphatic leukemia (CML, CLL))?
- Why do we not use available molecular-biologic technologies, particularly, cellular secretome analytics, epigenetics and molecular imaging, to systematically describe normative notions of tumor systems, which are featured by morphologic tumor structures, multifold rationalized action norms, and tumor-specific decision maxims (nodes, hubs)?
- Why do we still focus on communication lines and communication mediums (e.g., genes and specific steps in signalling pathways), although evolution is simultaneously characterized by evolutionary restricted communicative expression of communication lines based on differential rationalizations as well as by tumor-immanent normative notions?
- How useful is it, trying to transfer knowledge about timely and locally restricted validities and denotations of systems objects (objects' references, communicative expression), i.e., cells, oncogene-addicted pathways, etc. into completely novel evolutionary systems stages, which are characterized by the capability to establish novel stage-dependent communicative expression of tumor systems' objects? Evolving systems redeem modularly constituted background knowledge, which finally establishes communicative expression of systems objects (object-subject-relation).
- Why do we not comprehend respective tumor systems objects as being subjected to tumor systems-derived validity claims? The evolutionary mechanism of cancer is suggested to equally cover all cellular and molecular mechanisms.

From Evolutionary History to Evolution Theory

The introduction of a cancer evolution concept at earlier time has failed to revolutionize cancer research [2]. One important reason is the missing conceptual separation of an evolution history from an evolution theory. The two pillars, evolutionary history and evolution theory have to be separated according to their basic intentions.

Darwin recorded the history of evolution as a **continuous process of learning** to explain the spin-off of novel systems functions. This approach guides to Darwin's own universal system of 'evolutionary' science, a history of problem solutions during millions of years (Darwin C. On the origin of species by means of natural selection, or the preservation of favoured races in the struggle for life. John Murray, London 1859).

Tumor development can be considered as an evolutionary process within a temporally circumscribed and assessable observation period: Cancer represents the largest genetic experiment ever conducted. Distinct acquired genetic lesions are not distributed at random in tumor cells, despite the high variability of cancer causes, the heterogeneity of observed genetic aberrations, and the divergence of morphologic characteristics of diverse tumor types. The non-random distribution of genetic aberrations might be explained by the fact that cancer-associated dysregulated transcription factors (non-oncogene addicted factors) must still collude in a life-maintaining manner for cancer cell self-renewal, for proliferation, and for the build-up of a cellular infrastructure suitable to maintain normative notions for tumor promotion [3]. But how can we use multifaceted and scientifically well proven 'narrative' presentations of classic evolution models to describe tumor pathophysiology? How can be an evolution theory successfully implemented to design novel therapy strategies for metastatic tumors? Are evolution-adjusted pathophysiological considerations suitable to open up novel paths of heretofore unexplored therapeutic options?

Evolutionary History

Evolution History and Tumor Pathophysiology

According to evolution historical considerations, evolution is represented by 'narrative' presentations. In 'narrative' presentations, theoretic knowledge—mainly reductionist and contextualist derived—is solely intentionally used, but primarily not organized. At best, the benchmarks are scientifically proven, i.e., 'genetic progression', 'facilitated variation', and 'genome theory' etc. [2, 4, 5]. Consequently, a tumor system develops on the basis of 'narrative' presentations oriented at suggested normative notions, for example 'adaptation', 'learning', 'contingency programming', 'instigation', and 'spin-off of novel systems functions'.

Evolution historical descriptions on tumors are representing action-associated knowledge, derived from scientific experiments and clinical data, acquired in distinct evolutionary constrained systems, for example in vitro systems, animal or clinical models. 'Narrative' normative references, which necessarily constitute the frame for respective considerations, do not exclude any scientific object from the daily experience [2, 6–10].

Competition about normative references is standing to reason as mechanism for decision making. Such a particular communicative procedure has been delineated as universal principle from 'narrative' descriptions. Selection processes are

assumed to be initiated for accomplishing normative notions, for example 'self-interest', 'supply', 'demand', or also phrased the 'invisible hand' [11]. Selection of a distinct normative benchmark ensures the particular character of each description. The position of a comparative event is occupied by a normatively characterized state of equilibrium (homeostasis), which a distinct system 'selected' for resolving a particular problem.

Success and failure are mirrored in processes of competitive interaction. These interactions represent attempts to resolve problems and are described on the basis of a suggested underlying matrix facilitating learning processes. 'Learning' systems subjects, i.e., cells, pathways, genes etc., are obviously able for 'innovative solutions' of particular problems. Frequently, arbitrary and not scientifically proven normative notions serve as benchmarks for competition and selection.

On the background of evolution historical considerations tumor development may be considered as a continuous selection process:

Accordingly, cells in pre-malignant lesions evolve by natural selection [2, 8, 9, 12, 13]. This is suggested to account for how cancer develops from normal or molecular-genetically altered to malignant tissue. This multi-step process of tumor evolution serves to explain the difficulty for achieving cure, especially in the metastatic stage.

The reductionist model relies on three necessary conditions for the procedure of 'natural' selection, all of which may be found in tumors [12, 14]:

- Genetic variation in the tumor cell population [15]: Neoplastic cell populations may present as mosaics of cells with both different genetic and epigenetic changes that distinguish them from normal cells. Mutations arise irrespective of the current adaptive needs imposed by the environment [16].
- The novel acquired genetic variations may not compromise heritability [13]. When a cancer cell divides, both daughter cells inherit the genetic and epigenetic abnormalities of the parent cell, but may also acquire new genetic and epigenetic abnormalities due to genetic instability [7].
- Each genetic variation must affect survival or reproduction (fitness) [14]. While many of the genetic and epigenetic abnormalities in neoplasms are probably less contributing to evolution, others have been shown to alter important normative notions, aiming at increasing the proliferation rate of the mutant cells, or at decreasing the rate of cell death (apoptosis).

The evolutionary mechanism of cancer can be descriptively comprehended as a multistep event corresponding to the chosen and scientifically accessible normative frames. Multifaceted starting points for descriptions of evolutionary processes can be chosen, as evolution historical descriptions are representing action-associated knowledge [2, 17]: Multilevel selection processes; stress-induced genome system instability (the diverse causes of cancer) [7, 18]; 2-hit hypothesis for mutation [19, 20]; genetic instability and natural selection [10, 21–23]; loss of heterozygosity; somatic evolution in progression, based on a series of genome system replacements [24]; senescence [25]; genetic heterogeneity in neoplasms [26]; somatic evolution by epigenetics [27]; clonal expansions [28]; phylogenetic analyses [29, 30]; adaptive

landscapes [31, 32]; the hallmarks of cancer may be considered as evolutionary adaptations in a neoplasm [33].

Reconstructive efforts on the basis of evolutionary historical considerations have to deal with incommensurable scientific levels and with 'learning' processes. All these reconstructive approaches necessitate hierarchical and unidirectional evolutionary processes as the 'metabolism' of evolution [34]: Evolution can be assessed with rationally reconstructible patterns, which correspond to a hierarchy of more and more complex structures. Just this hierarchy is raised to question when communicative processes are considered as a valid basis for explaining developmentally founded tumor processes.

Models of rational reconstruction within an evolution historical frame can be suggested, if an innovative achievement may be denoted for a complex learning process. As such models admit a clear normative reference and action-theoretical interpretation; they may be used for narrative presentations. Accordingly, the history of evolution is rich in descriptions, which may serve as example for rational reconstructions of evolutionary processes. In all cases the reconstructions bargain for narrative presentations despite of the underlying rational models, as they tell us about 'attempts to resolve problems' in an evolutionary context.

The genome theory of cancer evolution, for example, introduces networking interactions of genes driving tumorigenesis [35]. However, with an exclusively functional consideration 'rewiring makes the difference' [36], the systems-associated constrictions of gene and cell functions, which take place in cell systems during evolution, are misplaced from the perspective of an observer to the level of communication by tethering inter-systemic exchanges at imbalances in communication. Thereby, the importance of the identity-threatening deformation of tumor systems is withdrawn [3].

Multifaceted combinations of molecular mechanisms, available alternative pathways and compensatory changes of protein expression can result in unmanageable complexity. Therefore, it is important to move research from the characterization of individual molecular (genetic) mechanisms to the understanding of the overall system behavior during cancer evolution. Particularly, the gene-centric thinking is moved to genome-centric thinking (genome theory) [35].

Current systems biological considerations rely on studies of basic science, which primarily try to disassemble complexity and measure the activity of isolated systems components in a distinct evolutionary context. Such an approach is very successful in characterizing the individual parts but very limited in reconstructing and predicting how single components are communicatively integrated and rededicated within novel systems contexts (modularity): Depending on the host, the developmental status, and the particular systems contexts, genes and their gene products may have completely different, sometimes opposing functions. A prominent example is p53 [37]. Obviously, the communicatively linked biochemical or cellular background may define validity and denotation of distinct systems objects, for instance in case of transcription factors. The term 'oncogene' does not cope with the evolutionary or therapeutically induced function of a distinct gene.

Evolution History and Tumor Therapy

The necessity for moving from evolution historical narrative to evolution theoretical considerations (evolution theory) for bridging theory and therapeutic practice may be exemplarily highlighted by common observations revealing discrepancies between therapeutic theory and practice [38]. Phrasing obstacles for translational research based on evolution historical considerations in the clinical field allows focusing on issues that have to be covered by novel hypothesis-triggered methodologies (evolution theory). At this stage, a formal pragmatic communication theory points up to the reconstruction of communicative relations among systems objects (pathways, molecules, cells, etc.) [39].

- Clinical trials do not need to unanimously re-confirm the non-transferability of reductionist, context-dependent knowledge (evolution historical knowledge) to completely novel evolutionary systems contexts in metastatic tumor. Doubtless, systems objects and communication lines, as the benchmarks of communication, may have one striking common feature in various preclinical systems contexts or in novelly evolving tumor systems: A therapy-relevant systems object may be successfully proven, quantitatively and qualitatively, including all its variations, up- or down-regulations, and molecular modifications. However, targeting a specific molecule with the scheduled 'targeted' drug or drug combination may lead to differing or unexpected results in tumors with different evolution history [40, 41]: Multifaceted chromosomal or molecular-genetic aberrations, in tumor cells, but also in stroma cells, ultimately determine the communicative expression, i.e., the meaning of systems objects, in a therapeutically relevant way.
- **Nonlinear responses** of differentially developing tumor systems are a well-known phenomenon: Philadelphia positive chronic myelocytic leukemia may be livelong controlled in more than 60 % of patients by inhibition of chimeric tyrosine kinase [42], while additional aberrations in CML disease often result in loss of disease control by respective targeted therapies [43]. Sorafenib, another tyrosine kinase inhibitor, is weakly active in combination with chemotherapy in Flt-3 positive acute myelocytic leukemia (AML), but administered as a single drug, it may induce continuous complete remission in patients with Flt-3 positive AML, relapsed after allogeneic stem cell transplantation [40, 41; Chap. 7]. Exclusive targeting of tyrosine kinases in a distinct evolutionary systems context may lead to a complete redirection of a systems' normativity in Flt-3 positive AML, relapsed after allogeneic stem cell transplantation: The systems' perturbation depends on the kinases' communicative systems context.
- Data derived from **high-throughput arrays** or *in silico* approaches contribute to uncover novel therapy approaches, for example combined single-track therapies ([44, 45]; Chap. 2): Their maximal beneficial yield has not yet been reached. To overcome problems with combined single-track therapies, it is necessary to process quantitative proteomic data from appropriate hypothesis-driven models. Evolution-adjusted tumor pathophysiology provides the necessary diagnostic instruments for modeling drug effects [39, 44, 46–49] by introducing

the reconstruction of tumor-promoting rationalization processes. Rationalization processes represent the multidimensional networks available for constituting tumor-promoting normative notions, i.e., angiogenesis, immune response etc.

- **For the long-term therapeutic management of metastatic tumors**, it is important to formally establish the therapeutically accessible, evolutionary restricted operative scope of tumor systems by using appropriate diagnostic steps (cellular secretome analytics, molecular imaging) [50–52]. Reconstructing systems objects' validity claims, that means assessing the communicative expression of systems objects within a distinct evolutionary context, is feasible and enables to better understand and target the communication-derived tumor pathophysiology. The available novel diagnostic repertoire will facilitate the appropriate selection of technical instruments for successful biomodulatory interventions, defined as cellular therapies in situ.

The operatively accessible communicative benchmarks are endogenously developing, but also—as shown—accessible for therapeutically evolving normative systems features (Chap. 19). The communicative benchmarks in tumors are established by a broad spectrum of acquired rationalization processes, which are provided for establishing a pattern of tumor-type and stage-specific normative notions.

As shown in clinical trials, attenuating tumor growth can be realized by biomodulatory therapies via implementation of non-normative boundary conditions into the tumor's normative systems structures [46]. Biomodulatory, primarily multi-track therapies are focusing on the evolutionary derived systems stage and are not primarily oncogene-addicted or theme-dependent targeted therapies, such as single- track ('bottom-up') approaches (Chap. 22).

The two methodological pillars, either reductionist or holistic procedures, for creating evolution-adjusted tumor models are supplementary as the benchmarks of communicative systems correspond to the components of which functional sequences are composed. From different methodological viewpoints, the total extensiveness of tumor pathophysiology may be highlighted only now and in such a way that would be desirable for the development of **one individual tumor therapy (personalized tumor therapy).**

However, by exclusively using evolution historical considerations, we cannot obtain the conceptual equipment for action-theoretical abstractions (biomodulatory therapies), for the assessment of systems-associated tumor stages or for the systematization of rationalization processes (communication-derived pathophysiology) based on an adequate differentiation between:

1. Synchronous structural differentiations of the functional 'world' of tumor-associated cell systems,
2. The spin-off of functional systems that are differentiated via chemokines and cytokines as well as the interior differentiation of these cell systems (e.g., accumulation of regulatory T-cells, mesenchymal stem cells), and
3. The differentiation processes induced by tumor cells, which simultaneously dedifferentiate differentiated cellular functional areas (rationalization of functions) in terms of a colonization of the functional 'world' of organ tissues (metastatic

process), simultaneously facilitating the integration of new cellular elements from the peripheral blood (mobilization, trafficking) [3].

Evolution Theory

The following evolution theory is based on the assumption, that biological processes are interwoven with communication and are represented and reproduced through communication acts to facilitate communicative expression [39]: A tumor system not only consists of diverse cell types and pathways, the so called tumor systems objects, but also comprises all components of action insofar that these components are oriented in terms of diverse cell types. The components of action are organized in communication acts.

Communication within a biological system is closely linked to the descriptively accessible 'learning' processes, to contingency programming, adaption of the multifold 'players', i.e., the systems objects within a tumor system [3]. An evolution theory should operationalize the 'metabolism' facilitating the spinoff of novel systems functions and is aimed at covering some practical, i.e., diagnostically and therapeutically relevant issues to convince the scientific community that the evolution concept is under-appreciated in the cancer field, both for diagnostic and therapeutic issues.

For many diseases, such as metastatic tumors, that have undergone umpty years of evolution, stepwise and evolution-adjusted therapy may be an alternative way to achieve medical improvement rather than drastic therapeutic interventions based on theme-dependent knowledge [53]. Thus, it is necessary to decode paradox situations of cellular rationalization, deformation, and communication processes or, in other words, to uncover inconsistencies within tumor cell compartments or distinct topologies of aggregated action effects.

Experimental Evidence for Communication Processes as Essential Part of an Evolution Theory

The following experimental and clinical data favor a **formal pragmatic communication theory** as a major element of an evolution theory into tumor pathophysiological and therapeutic considerations:

- **The distribution pattern of metastases** for solid tumors is not random. In 1889, Paget analyzed for the first time metastatic spread in autopsies from breast cancer patients and proposed that particular cancer cells or 'seeds' would only colonize receptive 'soils' [54].
- **The metastatic pattern:** A mathematical analysis, performed by Medicare in the U.S. on the basis of claims from over two million elderly American patients, enabled to reconstruct network models to analyse progression dynamics of cancers, based on their sites of origin. These networks were sufficiently robust to make

retrograde predictions of primary histological tumor types, given a metastatic pattern, and anterograde predictions of future sites of metastasis, given an individual primary site [55].

- **Besides hemodynamic factors, vascular and lymphatic drainage patterns** of a given primary site, additional 'forces', are implicated in directing tumor spread [56].
- Results on the molecular mechanisms underlying metastatic tropism seem to support the concept of the **'metastatic niche'** [57].
- **Autonomous and non-autonomous portions of transcriptional activation** in tumor 'stem cells' are accountable for differential tumor phenotypes and visualize the intersubjectivity of communication during tumor development (MDS, AML) [58, 59]. The nature of cancer stem cells may be considered as a state rather than an entity [60].
- **On a genetic scale**, each tumor presents a form of disease never encountered clinically before [61]. Despite the acknowledged tumor heterogeneity on a genetic scale, tumors are supposed to become 'eradicated' by targeting distinct non-randomly occurring oncogene-addicted events [38]. Efforts for personalizing tumor therapy are propelled by meeting genetic heterogeneity with selected single-track or combined single-track approaches (Chap. 22). Discounted is the normativity of cancer tissues, which share substantial phenotypic similarities (normative notions and corresponding rationalizations), despite the fact that the genetic paths to particular phenotypes are highly heterogeneous.
- **Convergent evolution** [61]**:** In cancers, distinct normative tumor-associated benchmarks promoting evolutionary processes are enabled by a large number of diverse, but non-random genetic changes [62]. Cancer diseases show convergent evolution for constituting tumor-immanent normative notions, as indicated for example by 'chronic' or 'acute' diseases: Cancer cells develop from all tissues, and the genetic basis is rather heterogeneous. Nevertheless, cancer tissues exhibit a scientifically accessible tool of reconstructible tumor-immanent normative notions (structures, functions and decision maxims), which are constituted by a wide range of rationalization processes. The multifaceted rationalization processes are frequently based on evolutionary mediated shifts in systems objects' validity and denotation. Evolutionarily altered validity and denotation seems to be the main reason for the frequently observed poor therapeutic accessibility of tumors treated with reductionist therapy approaches ('bottom-up' strategies).
- **Understanding fundamental properties of non-hierarchically organized operations in malignancies** is a crucial step for providing insights into novel therapeutical approaches [63]: Rubin and Raaijmakers reported changes in skin and bone marrow fibroblasts prior to the onset of visceral cancers and myelodysplastic syndromes/acute myelocytic leukemias, respectively [58, 64]. The results of these studies suggest that a 'systemic event'—representing a reason for an evolutionary opportunity within the tumor's 'living world'—may provide the first step for carcinogenesis (Chap. 23). The description, that interactions of cell autonomous and microenvironmentally determined events support the development of malignancy, e.g., during the evolution of myelodysplasia and consecutive acute

myelocytic leukemia, points to a communicative aspect [58]. This murine model of leukemogenesis also suggests non-random aberrations in mesenchymal cells as cause for tumor induction in heterologous cell types (hematopoietic cells).

- **Mathematical descriptions**, which aim at studying and designing the dynamics of tumor cell escape from selection pressures (intrinsic drug resistance), are hypothetically based on multi-type (Darwinian) branching processes [65]. These theories neglect the dynamics of reciprocally systems objects-intended criticizable validity claims [66]. For establishing normative notions, the frequently applied game theory decisively restricts an action-oriented theory, which is aimed at reaching 'understanding' [67].
- **An important observation contradicting the Darwinian selection processes** ("selection of the fittest") describes how evolution-promoting processes (genotoxic stress) are translated into digitalized, reproducible genomic structures in prostate cancer cells [18]: Novel findings elucidated several unexpected general principles for non-random chromosomal translocations in tumors. 'A long-standing concept in tumor translocation has been that genotoxic stress causes direct random double strand breaks (DSBs) that lead to random translocations, with the 'selection' of those conferring growth advantages. By devising and investigating a model of tumor translocations that fully mimics the frequency of in vivo events without proliferative selection', Lin et al. suggested that 'there is a site-selective immediate pattern of DSBs that ultimately 'dictates' the pattern of tumor translocations' [18].

Most studies on somatic cell evolution are limited to the level of genes, their variants and their expression levels. Such single gene analyses, likewise whole genome analyses, cannot per se assess how single aberration patterns collude in a life-maintaining fashion as prerequisite for a **'macroevolution'** that is suggested to drive cancer evolution [23]. The common, but highly heterogeneous patterns of 'genome system replacements' during tumor evolution support the concept that karyotypes define tumor systems; and that karyotypic evolution is a key event in cancer evolution.

However, an equivalently important evolutionary key event is the fact that histologically different cancers exhibit **convergent evolution** for constituting distinct normative systems features. Convergent evolution is facilitated by multifaceted rationalization processes supporting and maintaining phenotypically characteristic normative notions. The observation of multiplicity in acquired genetic aberrations and a comparatively restricted tool of rationalization processes for constituting convergent evolution pioneers the way for a formal pragmatic communication theory [39]: Acquired chromosomal aberrations are communicatively assigned for their situative validity and denotation within an evolutionary confined system by the holistic communicative context (tumor's living world'). The systems-mediated, therapeutically relevant reference of a systems object is not necessarily predictable from available systems objects' 'historic' references (evolution history) [18]. Further, the fact, that validity claims of systems objects are therapeutically criticizable by implementation of non-normative boundary conditions (biomodulatory therapies), demonstrates evolvability of evolutionary constrained systems levels.

Benchmarks of a Communication Theory as Essential Part of an Evolution Theory

Therapeutically efficacious access to metastatic tumors by combined modularized therapies (Chap. 2), emerged as a trigger for the problematization of established tumor models. Traditional models are based on reductionist or contextualist interpretations of metastatic tumors. However, these models may not explain the observed and therapeutically relevant activity of biomodulatory therapy approaches, which include drug combinations with only poor single agent mono-activity or none at all [46]. The routine reductionist perception of metastatic tumors lost its conversance and universal validity [66].

The presented evolution theory is based on observations derived from the successful implementation of biomodulatory therapy approaches for therapy of metastatic tumors. The resulting formal pragmatic communication theory connects all acquired data, provides an explanation that covers all gathered facts about convergent evolution and provides the basis for predictions [68].

Problem solution, which is orientated at suggested normative references (selection), is now contrasted by an evolution theory describing the 'metabolism' of evolution in form of communication-associated rules [69].

By introducing a pragmatic communication-theoretical approach, the intentionally defined normative notions, at which selection processes slave away, are resolved in equivalent communicative rules bent on the respective systems objects. Now, the socially interwoven tumor and stroma cell community evolves as a holistic communication-driven structure, which provides internal access, for example via modular therapy approaches. Thereby, systems disclose their modularly designed architecture and recon tumor tractability via modular structures [68].

Pragmatic Virtualization of Communication Acts

Modularity (Object-Subject-Relation)

In the formal pragmatic communication theory modularity describes pragmatically the object-subject relation, which is constituted between the two poles, the systems objects' functional world and the respective biological system's world [66]. Clinical efficacy of biomodulatory therapy approaches (combined administration of drugs with poor or no monoactivity) may be explained by evolvable modular systems structures bridging the requirements of a systems object ('historical' reference) and the communicative systems context [70].

Now, modularity is more broadly defined as an inherent feature of each systems object. Modularity does not describe rationalization aspects (structural and functional organisations of normative notions) to comprehend for example pleiotropy,

heterogeneity by constituting variational 'modules', functional 'modules', and developmental 'modules' [71].

A module, in the current understanding of the formal pragmatic communication theory, allows comprehending the communicative expression of a particular systems object and is part of a rationalization process for a distinct normative notion. In so far, 'modular structures' may facilitate evolutionary development [72]. Cellular functions, such as signal transmission or cell cycle control, are carried out by 'modules' made up of small networks, which are composed of numerous interacting molecules, which determine the systems participator's communicative expression.

Modularity, which places systems objects as situative subjects, implicitly imparts a certain degree of evolvability to systems by allowing specific modular features (i.e., modular communicative networks) to undergo changes with regard to validity and denotation of systems objects without substantially altering the functionality of the entire communicative system (robustness of the tumor's living world). Modularity may allow the retrospective establishment of spaces for evolutionary developments if modular events (therapy) are implemented. This way, the tumor's living world turns into a scientific object that becomes accessible for experimentally or therapeutically designed modular approaches for uncovering the tumor's modularity, the modular knowledge of each systems object [39].

Modularity of cells and cell systems is a ubiquitous intrinsic biologic dimension, which becomes of exceptional interest during evolutionary processes, for example during tumor growth. It may establish multi-functionality and evolvability within a holistic communicative tumor cell system. Modularity either descriptively (modular therapy approaches) or mathematically seizes the phenomenon that the various, sometimes even opposing references of the systems objects are interrelated situational biological stages, i.e., they are embedded in the communicatively arranged validity and denotation of systems objects [53].

Proteins are traditionally characterized based on their individual action as enzymes, signaling molecules, or structures constituting specific aggregates in cells. At this stage, the post-genomic view expands the role of proteins as an element within a network of communicative interactions [73, 74]. A more abstract term for a protein—in a communicative sense— is 'systems object', which acquires contextual functions within circumscriptive functional modules or within the holistic communicative network of a tumor system [75].

Cell communities and cells constitute themselves, alternating in a close modular response to informative processes (biomodulatory therapy, gene transfection etc.). Therefore, modular communication is usable as an internal systems-relevant and environmental communication mode: The evolutionary link between two different 'worlds' may be successfully constituted by a formal pragmatic communication theory defining rules and evolutionary constraints.

Background 'Knowledge'

Background 'knowledge' reassures systems robustness as illustrated by recovery from reductionist therapeutic interventions for tumor control. Tumor's robustness

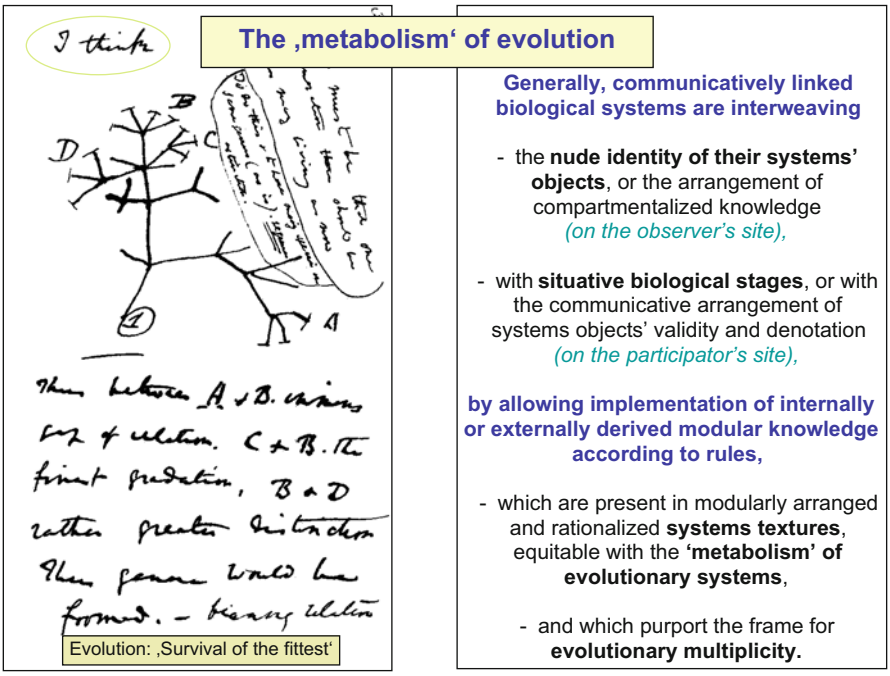

Fig. 12.1 Charles Darwin's 1837 sketch, his first diagram of an evolutionary tree from his First Notebook on Transmutation of Species (1837). Within reductionist considerations selection processes are indispensable. Modularity and rationalization processes, as discussed in a formal pragmatic communication theory, are sufficient to operationally define evolvability, which includes failure, fallacies, inconsistencies and rationalization processes. Tumors equip a biologically possible validity pegged to systems objects with the strength of facticity ('corrupt' rationalizations) under the conditions of a perceivable incompatibility between facticity and validity. Between these conflicting priorities the tumor disease is unfolding and 'branching'. Such a communication based definition of the term tumor disease refers to the polarization between success- and integration-orientated behaviors in biological systems

may be specifically responsible for poor therapeutic outcome, and robustness may absorb severe therapy-induced toxicities in a patient's organism. Thus, as our idealizations reach communication competence, the cells' explicit knowledge, which relies on idealizations (theme-dependent context knowledge), and the risk-absorbing knowledge of the tumor's living world (mediating robustness and systems context) compete in the range of the background knowledge about the tumor's living world [39] (Fig. 12.1).

The Tumor's Living World

Tumors are characteristically composed of functionally rather heterogeneous cell populations, i.e., tumor and stroma cells. Despite the ostensible morphologic heterogeneity of these cell populations, clinical trials using biomodulatory therapy

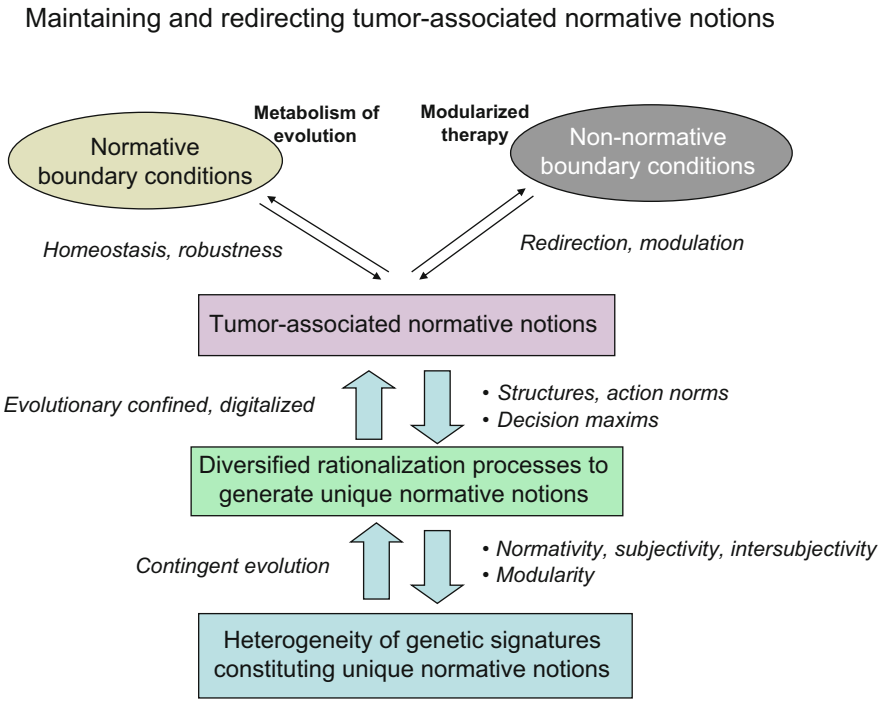

Fig. 12.2 For many diseases, such as metastatic tumors, that have undergone umpty years of evolution, stepwise and evolution-adjusted therapy may be an alternative way to achieve medical improvement rather than drastic therapeutic interventions based on theme-dependent knowledge

approaches have shown that these heterogeneous cell communities constitute a holistic, therapeutically accessible communicative entity [66]. Although this seems to be a contradiction at first, holistic communicative processes—termed the tumor's 'living world'—turned out to be a novel scientifically and therapeutically accessible object offering insights into evolutionary processes. Biomodulatory therapy approaches bring transparency into holistic communicative systems by breaking into a tumor's 'living world' and by dissecting a tumor for practical purposes, such as the attenuation of tumor growth (normative notion), in comprehensible evolutionary processes [39] (Fig. 12.2).

The 'living world' of the tumor provides the background knowledge, as it comprises the tumor's holistic communication processes, which we rely on in every therapy. The living world of morphologically defined tumor cell systems creates the term opposite to those idealizations, which originally constitute scientific (intentional) knowledge. The living world is uncovered by redeeming the validity of communicative tumor processes through implementation of modular knowledge of cellular and external environments (for instance for therapeutic requirements). Only experimental or therapeutic experiences (modular therapies) allow the separation of the tumor's living world into categories of knowledge.

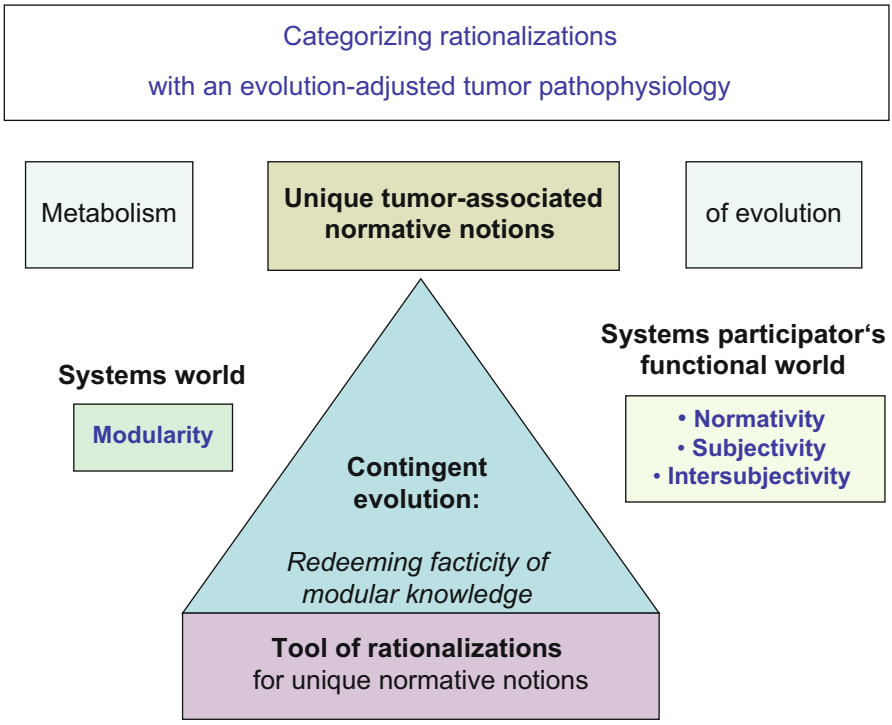

Fig. 12.3 The present evolution theory is based on the assumption, that biological processes are interwoven with communication and are represented and reproduced through communication acts to facilitate communicative expression. Rationalizations of normative notions are configured between the poles of systems world and systems participators' functional world with their respective communication derived rules

The newly uncovered systems perspective, which is frequently underestimated, moves its focus to the discrepancies that develop between the functional world of tumor-associated cell systems and the functional requirements imposed by rationalization processes and triggered by a tumor's systems 'world'. The (therapeutic) exploitation of background knowledge about the tumor's living world contributes to disrupting the holistic communicative thicket.

Perception of Validity

A significant difference exists between a communication medium (e.g., ion channels, molecular pathways, signaling integrators, cytokines, chemokines) or communication lines (e.g., gap junctions, signaling pathways, nerves) and the underlying communicative expression (purpose). Communication mediums and communication lines are assessed according to how well they technically work with regard to communication, whereas communicative expressions are evaluated according to their communicative validity (Fig. 12.3).

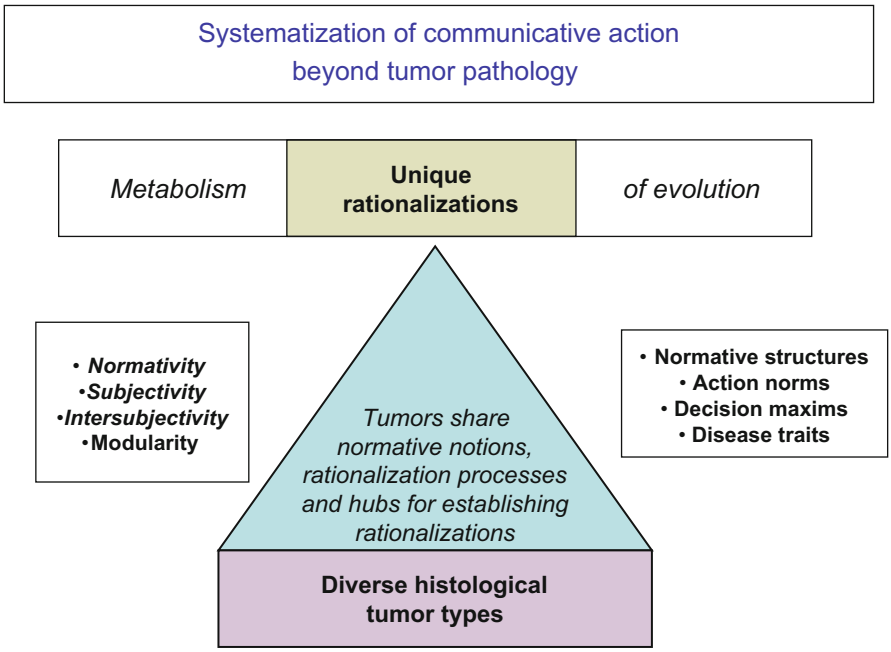

Fig. 12.4 Tumors share normative notions, rationalization processes and hubs for establishing rationalizations. Therefore, a novel categorization of histological tumor types is possible (evolution-adjusted tumor pathophysiology) according to shared tumor-associated normative notions and corresponding rationalization processes, evolutionary confined modular knowledge of systems participators and adaptive intersystemic exchange processes

Communication mediums and communication lines are easily accessible and comparable among rather different biologic systems. The reconstruction of their situative communicative validity and denotation—particularly in pathological circumstances (metastatic tumors)—necessitates further studies. These investigations should include not yet routinely operated methodologies, so that a distinct communication tool of interest can be assessed within its situational context.

Specific Conditions of Compliance Aimed at Redeeming Validity

Specific conditions of compliance aimed at redeeming validity are facilitating relations between communication technique (specified modular therapy approaches) and distinct tumor-associated situation-engraved systems stages. A holistic communication-based model now opposes reductionist systems views. The tumor's living world is, for example, uncovered by redeeming validity of communicative tumor processes through the implementation of modular knowledge in the cellular and external environment (for instance for therapeutic requirements): The tumor's entire communicative system is subjected to modular interventions pursuing the integration of complex biochemical systems processes (Fig. 12.4).

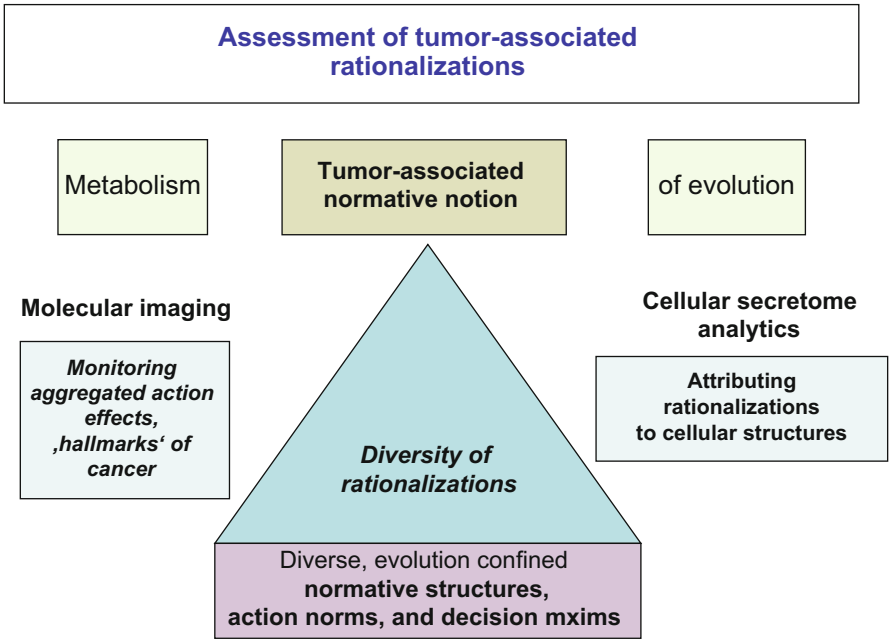

Fig. 12.5 Multifold technologies may be merged in a novel diagnostic setting to study the constitution of situative rationalization processes

Prepositional Communication Acts

Prepositional communication acts attribute validity and denotation to systems objects, constitute modules together with respective systems participators, and define the communicative expression of systems objects. The evolutionary communicative status is prerequisite for purpose-oriented (e.g., lineage fate, cell function) as well as communicative activities within the 'living world' [76].

Normative Biological Systems Structures

Normative biological systems structures include (1) cellular structures (morphological cellular and extracellular structures, including molecular-genetic or genetic aberrations, and modules), (2) compartmentalized action norms (diverse structures promoting angiogenesis, inflammation, immune response, robustness, cell death executing mechanisms, evasion of immune surveillance, glycolytic production of ATP also under aerobic conditions, the Warburg effect, compromised cell death programs, self-sufficiency in growth signals, tissue invasion, metastatic potential, limitless proliferation, stress phenotypes, such as metabolic, oxidative, mitotic, DNA damage stresses etc.) (Fig. 12.5), and (3) decision maxims (nodes, hubs) [33, 68, 77].

Of particular interest for the **preservation of normative systems structures** is the continuously proceeding process, through which internally- or externally-derived modular knowledge is implemented during the communicative exchange with the environment. The resulting situative communication profile enables—according to communicative rules—a steadily moving but distinct configuration of systems objects' validity and denotation, which is aimed at (1) maintaining robustness on the basis of definitely rationalized biological systems or (2) at rationalizing the tumor's living world to create non-linearly developing systems, i.e., tumor systems. In the course of evolution, the living world must be communicatively rationalized by the inclusion of situatively available or modified systems objects. Normative contexts limit the number of relations between the systems objects.

Rationalization of Normative Notions

In biological systems, modularity and rationalizations organize normative systems structures and interfaces for intersystemic exchange [66].

Rationalizations describe how normative notions of biological systems are temporally, structurally and functionally constituted (e.g., inflammation, angiogenesis etc.) and organized (intersystemic exchange processes) to achieve normative benchmarks. Purposes are enmeshed in rationalized 'life-forms' of communication-driven cell systems in a way that we cannot oppose or circumvent them (Chap. 23). A broad pattern of genetic changes and multi-faceted rationalizations converge to a limited pattern of normative tumor systems structures: Convergent evolution via rationalization of normative systems structures is a ubiquitous phenomenon [62].

In an evolutionary process, tumor cells may exploit the whole extent of the rationalization features of stroma cells to implement the functional diversity of systems behavior aimed at maintaining homeostasis and robustness in tumor systems. The implementation of a new form of integration (rationalization) of stroma cells allows the evolutionary advancement of the systems complexity with the remodeled rationalization of cellular functions: The diversified resources of tumor growth-promoting cytokines are distributed among rather different stroma-associated cell types (redundancy).

Tumor- and stage-specific therapeutic accessibility of normative processes to induce response in histologically rather different tumor types indicates differential integration of normative notions into the context-dependent 'living world' of tumor compartments and corresponding tumor-specific rationalization processes. For example, 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. Biomodulatory therapies, administered as fixed modules, may contribute to the discovery and understanding of novel regulatory systems in tumor biology [3] (Fig. 12.6).

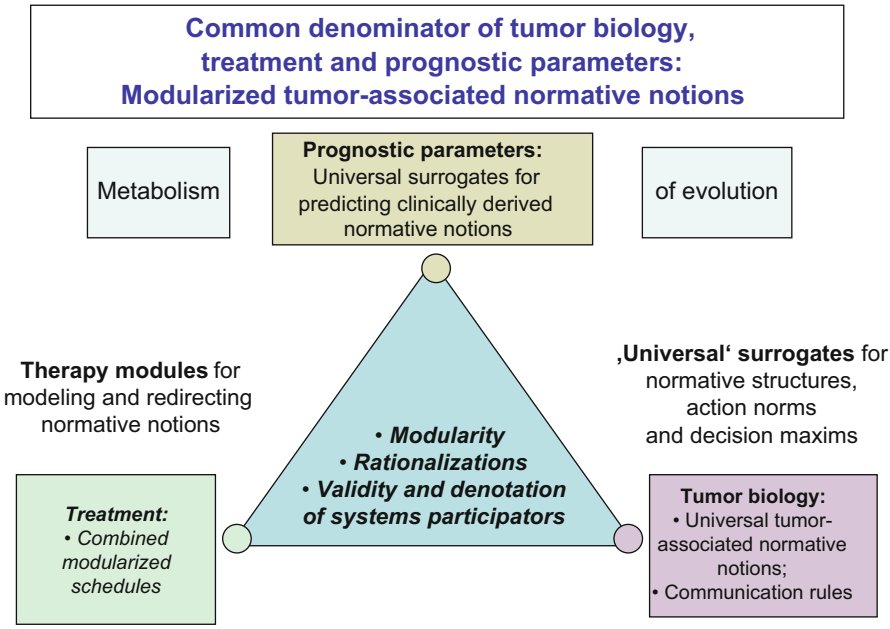

Fig. 12.6 Common denominator of tumor biology, treatment and prognostic parameters are closely interwoven tumor-associated normative notions. Tumor biology, treatment and prognostic parameters may be considered now from the perspective of consistent and inter-systemically comparable normative notions and make use of an integrative language

Intersystemic Exchange Processes

The complimentary reciprocal activity, which subsystems generate for one another, i.e., rationalizations, structures, action norms, and decision maxims, may be analyzed as currents of inter-systemic exchange. Therefore, from a therapeutic point of view, the systems biological model does not specify whether a normative notion has to be suppressed or stimulated to achieve tumor control: Inflammation control as well as stimulation of inflammation may control tumor growth, immuno- suppression, and immune stimulation. Contradictory decisions could be associated with the same capacity to achieve tumor control in a distinct tumor type [3] (Fig. 12.7).

Cellular Communication Acts

Cellular communication acts implementing redirection of modular events and rationalization processes do not generate experiences ('problem solutions'), but a **relief of activity**. Action systems may be rationalized with evolutionary constraints, in non-deterministical manner and in multifold directions [58].

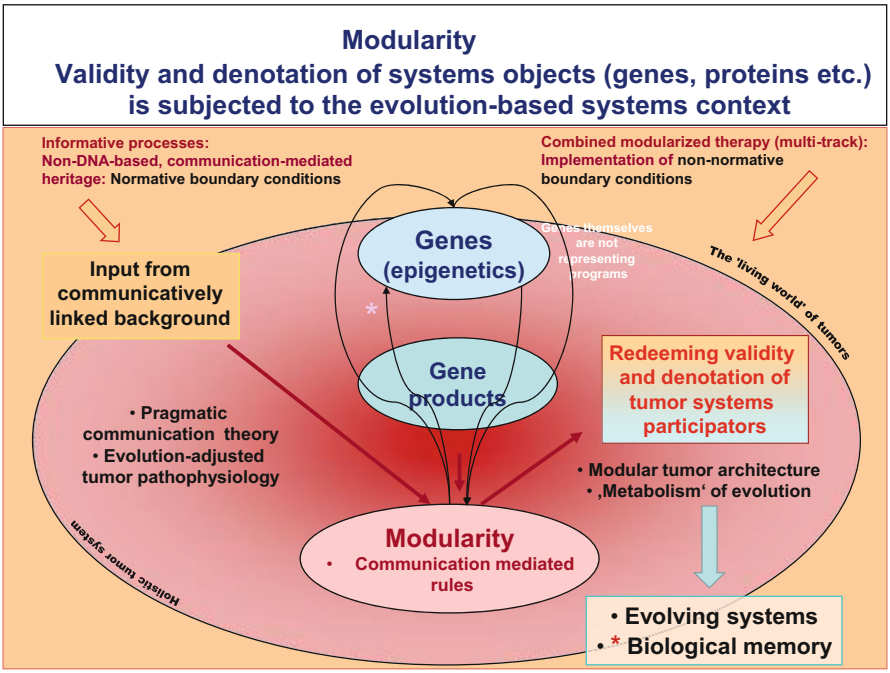

Fig. 12.7 Tumors allow experimental therapeutic access from inside in a comprehensive and reconstructive way (systems view) via modular (biomodulatory) therapy approaches and may be described as evolutionary developing systems. Modular therapies evolve the informative background, which redeems validity 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

Normative Tumor-Associated Benchmarks in Evolutionary Processes

Cell communities and cells constitute themselves, alternating in a close modular response to informative processes. Therefore, modular communication is usable as an internal systems-relevant and environmental communication mode: The evolutionary link between two different 'worlds', that of a systems participator and that of a system may be successfully constituted by a formal pragmatic communication theory.

Identity

In a reductionist sense, the object-associated identity serves primarily as a descriptive distinction towards the 'alter', the other systems object. Identity of a new 'organ', a separated system, or systems objects ('actors') is defined ex post from the perspective of an actively participating molecular and cellular systems world. The object-associated identity serves as a descriptive distinction towards the 'alter'.

The systems-associated identity of an actor, as the originator of a spontaneously accomplished communicatively driven action, may be only retrospectively assigned to already established identities (modular knowledge). The identity of an actor only occurs as a 'historical' feature. Identity is no inherent feature but is communicatively and situatively mediated, for example accomplished by the cellular fate within an evolving system [73]. The more evolutionary processes are involved, the more novel systems-linked identities of actors may be expected. Systems-specific redemption of validity and denotation is provided by the tumor's holistic communicative world, namely its 'living world' and endows identity, whereas noise, meaning that specific validity and denotation are not reified, does not specifically contribute to identity [66].

The claim for identity of rationality is confirmed in every ontogenesis (evolution history) [73]. In the systems-associated identity of an actor, as the originator of a spontaneously accomplished communicatively-derived action, the necessary structure of a subject and respective situative function are fused.

Robustness

Robustness (stability towards disturbances; complexity) and plasticity (switching to alternative rationalizations) may be described as rich branching (hubs!) and functional flexibility allowing dynamic switching of signals into alternative pathways in order to achieve nearly identical outcomes. Robustness is a fundamental feature of living systems. Evolution-trade-offs among the modalities robustness, fragility, resource demands and performance status provide possible benchmarks how biological systems evolve [78]: Multifaceted patterns of genomic alterations as well as diverse rationalization processes may initiate similar patterns of normative systems notions.

Tumor cell systems may recourse on differential rationalization processes (perlocutionary acts). Rationalization processes are symbolized by rather different communication lines and systems objects to maintain normative notions (robustness).

Basic mechanisms contributing to biological robustness are

- The steadily interwoven processes constituting the systems world and the functional world of systems objects
- The possibility to recourse on multi-faceted rationalization processes to fail-safe constitute normative notions
- Modular systems features by which a communication-derived decoupling from the former physical-chemical world may be established. The decoupling is based on the redirection of validity claims by communication-derived rules [73].

Local Penetration and Expansion (Colonization)

On the basis of the facticity of prepositional aspects, tumor cell colonization may lead to the complete destruction of non-regeneratory cell inventories. If 'traditional' organ-specific normative notions cannot be preserved, novel systems organizations

gain some kind of autonomy by neutralizing separation (identity) towards previous cellular functions or by the assignment of new functions [3].

Legitimation of Corrupt Rationalizations (Acceptance by an Established Organ)

Novel tumor-associated rationalization processes can be considered as strategies that allow systems objects and the respective modular arrangements to establish their 'corrupt' activities as justified, based on validity claims. Of interest are situative validity claims of a systems objects, which are grounded in the formal pragmatic communication theory and depicted with novel analytical approaches including mathematical specifications of 'modules' or functional 'fragments' [79; 80].

Participation in an Organ (Homeostasis)

Homeostasis—defined as the sum of processes available to maintain normative notions—can be explained on the basis of processes constituting robustness in involved organs and tumor lesions. Robustness is based on the multifaceted possibilities of systems objects to recourse on differential communication lines and rationalization processes to maintain normative notions. The impact of robustness in cellular systems, such as tumors, on the constitution of survival and reproduction is conspicuous. Robustness can be exemplified by therapy resistance in large series of metastatic tumors [81].

Redirection and modulation in systems rationalizations, induced by developing tumors, interferes with the affected organ and may destroy not-regenerative cell inventories. Thus, these changes not only alter previous ways of interactions among physiologic organ-associated cells, but also considerably affect the communicative infrastructure of rationalized communication within an affected organ. It is necessary to simultaneously decode paradox situations of cellular rationalization, deformation, and communication processes, i.e., to uncover inconsistencies within tumor cell compartments by means of a theory that includes the evolutionary development of a tumor as well as its biologic history in order to increase therapeutic options with systems-directed approaches.

Redistribution (Metastatic Process)

Each action system presents itself as an area of reciprocal interpenetration of subsystems. Each of these subsystems is specialized in reproducing basic functions facilitating tumor promotion. Successful tumor initiation is possible, if suitable normative boundary conditions, provided by the respective environment, prompt tumor cell proliferation, or if the tumor cell instigates a tumor-promoting stromal reaction. Non-normative boundary conditions might be responsible for insufficient communication with the tumor cell and consecutive 'smouldering' conditions or even tumor cell death.

Reproduction

One meaningful reproductive structure represents the genetic repertoire. The evolutionary reproductive function of tumor cells is underlined by molecular-pathologic data showing that molecular aberrations in the primaries determine tumor biologic behavior, for instance, early or late metastatic spread as well as metastatic sites [56].

The heritable inventory is evolvable via the tumor's living world [18]. This way, modular knowledge may be either incidentally or constitutionally acquired from the environment [18, 58]. Differential communicative interactions of environmental events with tumor cells results in molecular-genetic heterogeneity of tumors.

The second important reproductive structures are tumor-immanent rationalization processes (non-genetic equivalents to the genome): Despite of molecular-genetic heterogeneity in primary tumor sites or metastases, tumor-promoting rationalizations for normative notions are reproduced: Otherwise, we could not explain the successful modular access to metastatic tumor sites by implementation of non-normative boundary conditions. Biomodulatory therapies may induce continuous complete remission or long-term tumor control (Chap. 2). Reproduction of rationalizations has important implications for preventive strategies, for example in case of minimal residual disease, as well as for tumor control in the metastatic stage (Chap. 15, 23).

Combined modularized therapies show that modular events, assembled by the tumor's living world, are an additional evolution-constituting dimension, which is delimited by the respective aberrant genetic pattern, and the established tool of rationalization processes. Presumably, therapeutic redirection of the tumors' normativity is not based on genetic changes: Induction of biological memory might be an epigenetic process (Chap. 19).

Enhancement of Complexity, 'Corrupt' Rationalization

Tumor-related activities that seem to be operationally induced by the division of function, such as inflammation, neoangiogenesis, Warburg effect, immune response, extracellular matrix remodeling, cell proliferation rate, apoptosis, coagulation effects, etc. present itself from a systems perspective as an enhancement of complexity. Therapeutic efficacy of biomodulatory therapies has shown that tumor systems-directed therapies have the capability to use complex cellular communication acts as adjustable sizes to therapeutically modulate the tumor systems' stability, homeostasis, and robustness [46].

The formal-pragmatic communication theory allows the differentiation of the polarization between success-oriented and integration-oriented behaviors: Tumors equip biologically possible validities pegged to systems objects with the strength of facticity (corrupt rationalization) under the conditions of a perceivable incompatibility between facticity and validity. Between these conflicting priorities, the tumor disease unfolds and 'branches' according to rules that require further evaluation.

Stochastic principles or Darwinian selection models as a basis for clonal heterogeneity are commonly suggested as the driving regularity. At that stage, reciprocally acting communicative rules are added (Chap. 13).

Complexity may be explained as a function of modular knowledge and situatively available rationalizations to establish a **relief of function** within a systems context. If multifold prepositional communication acts are available for altering communicative expression of a communication line, modular knowledge may be implemented by redeeming validity and denotation of systems objects via therapeutically criticizable claims of validity.

The common starting point for understanding complexity is a phenomenon known as pleiotropy. Pleiotropy describes the observation that mutations simultaneously affect multiple normative notions. Experimental data reveal that evolution does not suffer at 'cost of complexity' because most mutations affect few traits and the size of the effects does not decrease with pleiotropy [82].

Relation Between Evolution Theory and Evolutionary History

Evolution theory cannot substitute evolutionary history, which is generated from a 'narrative' perspective, and which has to justify instructions for the solution of problems, and has to face aspects of criticism dependent on the chosen reference. Moreover, evolutionary history provides the basis for uncovering the rules of communicative expression linked to systems objects.

The necessary evolutionary historical constraints on retrospective explanations, i.e., selection, adaption etc., are relinquished by an evolution theory in favor of an in advance projected retrospective (prediction) derived from action-related, experimentally and therapeutically derived perspectives (e.g., biomodulatory therapies, efforts in transcriptional regulation, molecular imaging) [70]. The novel perspective may include particular claims on validity and denotation of systems objects within a novel evolutionary context, as well as evolutionary conserved communicative prepositions, which finally define validity and denotation within different evolutionary systems.

Evolution theories provide a basis for the therapeutic accessibility of evolutionary processes and an experimental frame to detect evolution-guiding communicative rules. They have no history and cannot be reproduced within narrative scenes due to their universal validity. The only restriction given: The contemporarily used communication tool is necessarily determining the answer of an investigated system, and the system itself is timely and locally positioned.

By introducing a pragmatic communication-theoretical approach, the intentionally uncovered structural levels are resolved in equivalent communicative structures linked to the respective systems objects. Now, the socially interwoven tumor and stroma cell community evolves as a holistic communication-driven structure, which provides internal access via modular therapy approaches, thereby disclosing its modularly designed architecture [39, 70, 83].

Communicative tumor (sub)-systems do not obey nominal conditions in an evolutionary process but adhere to rules to meet the validity of communication processes: Phenotypically distinguishable individual tumor disease may constitute within the predetermined range of—at least to some degree—autonomous tumor development. These self-evident presumptions compromise the phenotypical homogeneity of tumors. Induction of complete remission or long-time disease stabilization with combined modularized therapies, indeed indicate that rationalizations of normative notions within a tumor disease are frequently homogeneously organized (Chap. 2).

> How may be a theory about evolutionary processes ('metabolism' of evolution) linked with 'narrative' forms of evolutionary comprehension?

Theories about the development of distinct forms of behavior reductionistically undermine as hypothesis-driven theories (capable to explain experimental data) the traditional 'narrative' presentations about evolutionary processes.

However, starting point of evolution-theoretical considerations remains the reductionistically, in any arbitrary evolutionary system detected reference of a tumor systems object (cell, oncogene-addicted pathway, etc.) and the primarily hypothetically phrased tumor-inherent normative structure, to which a systems object can contribute.

Experimental or therapy derived data on communication-derived rules among tumor-associated rationalizations facilitate to resituate systems objects as systems subjects, which have been integrated in novel evolutionary based systems contexts. Evolutionary based communication-derived constrains may attribute tumor systems objects novel tumor type- and stage-dependent patterns of references, based on their modular knowledge.

Evolution theories or histories for describing tumor development should contribute to broaden the therapeutic instruments. The competing evolution historical and the evolution theoretical model systems show quite different model-creating determinants. Evolution theory may provide the basis to include non-oncogene addicted targets [38], and drugs with poor or no monoactivity into the therapeutic calculus and aims at targeting the tumor- and stage-dependent communicative expression, which is steadily involved in the 'metabolism' of evolution.

An Evolution Theory Provides the Scientific Tool to Answer Central Questions in Future

> May be an evolution theory consulted for the assessment of competing evolutionary histories about the same phenomenal domain?

By adding evolution theoretical considerations, tumor systems biology becomes an operatively accessible size. Evolution-adjusted tumor pathophysiology describes object-subject relations independent of the starting point, which is operated by evolution historical considerations. The main challenge for an evolution theory is

to converge the experimentally derived results, which have been generated ensuing from rather different experimental starting points (Chap. 22), and to describe communicative rules that are involved in tumor progression [66].

Competing evolutionary histories may be resolved by the introduction of communication derived validity claims of systems objects. Validity claims put communicatively linked systems objects in an evolutionary context. Validity claims of systems objects are based on communicatively derived pre-suppositions within a particular systems context, and they position preclinically-derived references of objects as situative systems subjects, which may be characterized by novel denotations in non-linearly evolving tumor systems.

The necessary structure of a systems subject and the respective situative function are fused in the systems-associated identity of an actor, as the originator of a spontaneously accomplished and communicatively-derived action. The novel 'selection' rules, based on modularity and rationalization processes may be uncovered by retrospectively establishing spaces for primarily non-heritable evolutionary developments, if modular events are implemented.

> May a universal history of evolution be described, which can be based on multiple particular descriptions of evolutionary solutions, or particular reconstructions of problem resolution?

A universal history may only arbitrarily approximate to the problem of the 'driving forces' of evolutionary processes, as selection processes always anticipate predetermined and often heterogeneous normative references. The 'metabolism' of evolution is experimentally (for example by gene transfection, knock-out models etc.), and in case of tumors also therapeutically accessible (biomodulatory therapies). General communication-derived rules assessing modular knowledge of tumor systems objects and the prepositional circumstances for a distinct communicative expression should explain multifaceted 'problem solutions'.

As rationalization processes are inherent in biological systems, inconsistencies, Achilles' heels, deformations or missing inter-systemic exchange processes are implicitly emerging features of such systems architectures: On this background, the claim for 'survival of the fittest' should be revised. 'Selection' in the Darwinian sense relies on reductionist based observations, which do not necessarily account for the 'metabolism' of evolution as the original texture. The Darwinian notion has originally established the fundamental biological feature, namely evolvability of communicatively linked cell systems. The assumption of modularity and rationalization processes is sufficient to explain that distinct tumor-associated genotypes may acquire stage- and context-dependent denotations, for example during the course of a tumor disease [40, 65].

> Is a formal pragmatic communication theory a methodological instrument to explain diverse ways of 'problem solutions' with unique scientifically accessible principles?

If we separate evolutionary structures (metabolism of evolution, modular knowledge of systems objects, communication rules, molecular genetics) as activities intending to transfer empirically derived objects into situative systems subjects, we do not need to establish continuity (unidirectionality), necessity or irreversibility of the course

(genomically induced aberrations), and selection to explain diverse ways of 'problem solutions'.

Competences of systems objects may be reconstructed only if they are therapeutically or experimentally accessible to the contemporary scientific objectivity.

An analysis of developmental logics may escape from fallacies, if the analysis does not inductively pick up the hierarchically arranged structural patterns ('ontologies'), but, if it systematically justifies that the respective 'higher', more complex niveau for 'learning' is based on the interaction of the holistically communicating systems world and the functional world comprising its systems' objects. Formally, there remains no space for 'superior' or 'higher' organization to the preceding one, but tumor-related activities achieve an enhanced level of complexity.

The inclusion of evolutionary based principles and communicative rules into the therapeutic calculus, i.e., modularity and rationalization processes, besides the whole genome analysis, allows to feature a stage- and tumor-type dependent personalized tumor pathophysiology and to set the stage to select among combined modularized tumor therapies, dependent on a tumor's genetic- and communication-derived systems status.

At this stage, the technical and theoretical instruments are available to explore, whether it is possible at all that the developmental logical processes (implementation of modular knowledge) and genome-based processes are not the same involving different levels of tumor systems alterations, as the genome theory is suggesting [2].

Environmental carcinogenesis may be explained with the presented evolution theory by continuous implementation of non-normative boundary conditions in biological systems, independently of the qualitative feature of the boundary conditions [84, 85].

Evolvability is commonly assumed as the ability to respond to a selective challenge by a genetically based phenotypic change [16]. The term evolvability is now extended to the non-genomic, but also digitalized working systems world of a cell: Systems objects are continuously exposed to modular events by externally (non-normative boundary conditions) or internally implemented (redeemed) modular knowledge (pathophysiological processes). Beyond the (molecular-) genetic heterogeneity of tumor cells at primary and metastatic sites, rationalization processes for tumor-promoting normative notions can be preserved (Chap. 2, [22]).

Accessibility of Evolutionary Processes (Communication Acts)

As nature is interwoven with communication and is represented and reproduced through communication acts, communication associated rules and constraints should be made scientifically accessible and reconstructible with appropriate methodologies:

- **Diagnosis of normative systems structures and there therapy-derived changes** (cellular secretome analytics, molecular imaging techniques, epigenetics of mononuclear cells in the peripheral blood, assessing rationalization processes of tumor-immanent normative notions) [50–52].

- **Comparative uncovering of tumor systems biology by** implementation of non-normative boundary conditions ('top-down', 'bottom-up' approaches, Chap. 22) and modular knowledge, with the aim to detect rationalization structures and intersystemic exchange processes [68].
- **Diagnosis of developmental problems in tumors:** Inconsistencies, deformations, aggregated action effects, Achilles' heels, robustness, i.e., multiplicity of available rationalizations to maintain normative notions [3].
- **Detection of communicative presuppositions**, which may facilitate evolutionary based, systems-restricted combinations of transcription factors on a genome-wide scale (modular knowledge), and which can specify regulatory elements ultimately responsible for both cell identity and situative cell type-specific response to diverse signaling inputs [73].

The newly uncovered systems perspective, which is frequently underestimated, moves its focus to the discrepancies that develop between the functional world of tumor-associated cell systems and the functional requirements imposed by rationalization processes and triggered by a tumor's systems 'world'.

Assessment tools of tumor systems biology are (corrupt) rationalization processes, inconsistencies, deformations (Achilles' heel), altered intersystemic communication, and the topology of aggregated action effects (enhancement of complexity), robustness (recourse on alternative rationalization processes), homeostasis, intersystemic exchange processes, reproduction (proliferation, apoptosis-resistance, dysplasia etc.), local penetration and expansion (colonization), and redistribution (metastatic process). The proof of discrepancies is suitable to identify communication-derived rules. Without these rules, evolutionary processes would not function [3].

Up to date, still insufficiently processed remains the evaluation of communication acts establishing identity (new 'organ', separated systems), legitimation of corrupt rationalizations (acceptance by an organ, factual acknowledgement of criticizable denotation claims), and participation of a neoplastic process in an organ (homeostasis). Interestingly, transplantable identity is not necessarily bound to acquired aberrations mediating neoplastic disease [86].

The therapeutically relevant acquisition of the 'language' of communicative cellular expression gives hints on the 'metabolism' of evolutionary tumor development. Supported by the therapeutic possibility to implement non-normative boundary conditions into the tumor' living world, the situative and specific redemption of validities of communicative processes may facilitate the promotion of a tumor's evolutionary development. The procedure is closely linked to the differential development of novel denotations of the systems objects: Via communication-relevant processes, systems objects are acquiring novel references within the tumor's living world without at first substantially altering the functionality of the entire communicative system.

Practical Relatedness of an Evolution Theory for Tumors

Communication Derived Tumor Pathophysiology

Assessment of Evolution–Mediated Rules: The 'Metabolism' of Evolution

Modular therapies exemplarily give indications of the 'metabolism' of evolutionary processes. Evolutionary processes are symbolized by redirected and modulated validity claims and denotations of systems objects, by object-subject-relations, by a realignment of normative structures, functions and decision maxims. The dissection of the holistic communicative tumor system in scientifically assessable systems terms advances the metabolism of evolution into the diagnostic and therapeutic focus [46].

Implementation of modular knowledge by primarily multi-track approaches ('top-down approaches'), such as combined modularized therapies, single-track approaches ('bottom-up' strategies), such as gene transfections, cell transplantations, cellular stress etc. may result in substantial evolutionary processes within the frame of the tumor's 'living world'. Non-normative boundary conditions, maintained by therapies, noxa or non-malignant processes (e.g., inflammation) have the capacity to induce molecular-genetic aberrations in tumor and stroma cells. Even transplantable non-malignant stroma characteristics may be induced [18, 86]. Vice versa, the (molecular-genetically altered) microenvironment facilitates clonal evolution of tumor cells [58].

All these therapeutically induced modular changes aimed at evolving biological systems are reproducible: This indicates that modularity and the **organization of rationalization processes is digitalized** and ascertainable in communication-derived rules. Digitalization does not exclude analogous working steps, for example represented by hubs.

The most important task for a communication-derived tumor pathophysiology is to look for common systems features within different tumor types to get action-theoretically guided classifications of distinct evolutionary systems processes. Furthermore, classification is essential because classification is the basic language of medicine and of systems organizations across different tumor types, which need to be clearly defined. The uncovering of common evolutionary features in different tumor types is only the beginning. Lymphomas could soon be classified according to their activation of inflammatory signaling pathways [87, 88]; common stroma gene expression sets may be detected in response to tumor invasion: and neoplasias may be classified according to their responsiveness towards combined modulation of transcriptional networking [46]. Another attempt may be the formulation of stroma scores or cellular secretome signatures [50, 89]. Tumor systems may be assessed according to rationalization aspects of normative notions—how are e.g., the hallmarks of cancer multi-dimensionally constituted, which cell types are contributing to a normative notion (Chap. 17)?

Systems that are based to a high degree on division of functions seem to be less susceptible to reductionistically designed therapeutic perturbations. Tumor cells in

such rather robust systems are characterized by multifold chromosomal aberrations [62]. Studying a tumor's robustness that means, assessment of perlocutionary processes supporting a normative notion will be of further therapeutic interest and could contribute to novel decision criterions for the selection of therapy. Failure of systemic standard therapies may be a measure for the resistance of these tumor systems towards external perturbances. Robustness is retained by the tool of the systems participators' background knowledge [90].

Evolutionary Reconstruction of Tumor-Associated Systems

Redeeming validity is tailored on the relation of modular communication to the objective features of the tumor compartment, the reconstructible evolutionary (modular) systems [68]. Modular events (biomodulatory therapies) serve as a prerequisite for the reconstruction of the tumor's living world, in which cells are symbolic communicative figures with—to some degree—exchangeable references connected by modular prepositional structures: Consecutively, communicatively derived systems may be described by rationalization processes, deformations, and intercellular exchange [3].

The application of available methodologies in novel indications, i.e., cellular secretome analytics, assessment of transcriptional regulation, molecular imaging etc., facilitates to decode paradox situations of cellular rationalization, deformation, inconsistencies, Achilles' heels of communication processes in the tumor cell compartments by means of a theory that includes the evolutionary development of a tumor as well as its biologic history: Aim is to increase therapeutic options with applied systems-directed therapies [3; Chap. 2]. In the mirror of evolutionary processes, the functional 'world' of cell systems may be recognized under systems-therapeutic conditions and vice versa [46, 91].

Situation-Related and Stage-Dependent Communicatively Explicable Evolutionary Constraints

Novel normative systems structures and rationalizations may evolve by continuous implementation of non-normative boundary conditions. Darwinian 'selection pressures' are depicted in an communication-driven evolutionary process by stage- and tumor type-dependent situative non-random communicative constraints (modularity, rationalization), by non-deterministic communication acts of systems objects, which are characterized by intersubjectivity, normativity, and subjectivity, and by stochastic communicative events (carcinogens, 'instigations', non-normative boundary conditions) [84, 92]. The availability of a **non-deterministic communicative window** again underlines the therapeutic accessibility of communication associated rules and constrains (Chap. 23).

In the initial development of pre-neoplastic lesions, cellular proliferation is controlled by communicative interactions with other cells, the extracellular matrix, and by soluble or insoluble growth factors [58]. Clonal expansion is permitted by gain of

function mutations in 'oncogenes', loss of function mutations in tumor 'suppressor genes', and disruption of normal senescence pathways. Evolution historical considerations provide explicit 'selection mechanisms' for single mutations, as indicated in the classical Fearon-Vogelstein model of colorectal carcinogenesis [93]. Vice versa, this model is indicative for a distinct feature of communicative rules, namely the availability of evolutionary conserved prepositions in a tumor systems context, which facilitate validity and denotation of tumor promoting communication lines. The evolution theory adds the non-deterministic communicative window, both for tumor development and for tumor control. Hierarchical organizations arise within the contextuality of validity claims of systems objects and may contribute in so far to the truncation of developments [94].

Definition of Evolutionary Conserved Communicative Structures

Hereditability of communicative presuppositions and consecutively of the systems objects' communicative expression is symbolized by evolutionary conserved communicative structures. Communicative expression is an inherent biologic feature of a communication line or a tumor-associated communication tool. The following prerequisites for the communicative exchange may release us from the necessity to evaluate communicative expression in a novel evolutionary context and may give hints for hierarchical orders: The availability of (1) universal suppositions for a distinct communicative expression of a communication line or medium, (2) the universal reciprocity of the communication act's immanent obligations, (3) universal clarifications of an intersubjective use of communication paths, (4) the possible universalization of action-associated norms (e.g., evolutionary conserved apoptotic pathways), and (5) the intersubjective commonality.

Whether communicative expression of a communication line is really **evolutionary conserved** may be assessed by evaluating the prepositions of systems objects' validity claims. The institutionalization of communication acts facilitates the attainment of evolutionary conserved, seemingly hierarchically organized systems. A communication concept, which enables the possibility for a generalization of prepositional circumstances constituting communicative expression, may be useful to evaluate legitimating-critical actions, e.g., cell fate determination. The development of multicellular organisms (tumors) is associated with complex rationalization processes for the relief of functions, and involves 'progenitor cells' endowed with evolutionary conserved complex communication concepts, which give rise to cell types with specialized functions (functional world) within a distinct systems context (systems world).

Implementation of communication-derived tumor pathophysiology in parallel to histopathology The classic methodology of pathology is comparatively classifying. The theoretical core is formed by assumptions about the structural differentiation of cells (histopathology) in functionally specialized systems of interaction. These assumptions are sufficient for supporting the observation that the

structural integrity of tumor compartments needs to be maintained to sustain appropriate tumor-stroma-cell communication for tumor progression. Thereby, functional considerations are not sufficiently separated from structural ones in such a way that the disposed concurrence between methodological strategies may unfold.

A further competitive research approach exclusively investigates the rationalization of functional systems in the course of evolutionary growth complexity during tumor development and tumor spread under the aspect of different purposes. The aspect of rationalization may be elucidated by the analytically defined functional spectrum (references) of fibroblasts or macrophages within a cellular system: Macrophages and other inflammatory factors do more than just foment angiogenesis in tumors, i.e., they actively aid cell movements that produce metastases, thereby calling tumor cells to the vessels. On the other hand, they may act as tumor-antigen presenting cells for tumor control. This out- lined functional 'world' of macrophages gives an impression of rather divergent options of rationalizations within a systems context.

A third approach pins down the tumor pathology at disordered intersystemic exchange processes, at the imbalance of mediators.

Each of these research approaches and viewpoints described brings about the separation of subject and object. In other words, none of the approaches considers it necessary to uncover the object. A tumor's systems biology is also a scientific subject, a co-subject of the scientist that interests not only as an approach for observation, description, and explanation of cellular behavior. Even more, it serves as a communication partner, for instance via biomodulatory therapies, and thus as an approach of hermeneutic comprehension. This approach represents a scientifically new aspect for understanding tumor biology, implicating a decisive broadening of therapy options that arise from the evolutionary consideration of tumor development [3]: **The systems objects' subjectivity is now scientific object** (Chap. 23).

Therapeutic implications of a communication derived tumor pathophysiology Criticizability of validity claims is the starting point for biomodulatory therapy approaches. Validity claims, which are generally associated with an action norm, may be solely redeemed with justifications based on the permissibility and the factual acknowledgement of criticizable denotation claims (subjectivity of each communication act): Therefore, single objects of a system share competences, i.e., **modularity, background knowledge, intersubjectivity, normativity, and subjectivity**.

The therapeutically relevant acquisition of the 'language' of communicative cellular expression gives hints on the 'metabolism' of evolutionary tumor development. Supported by the therapeutic possibility to implement non-normative boundary conditions into the tumor' living world, the situative and specific redemption of validities of communicative processes may facilitate the promotion of a tumor's evolutionary development. The procedure is closely linked to the differential development of novel denotations of systems objects: Via communication-relevant processes, systems objects are acquiring novel references within the tumor's living world without first substantially altering the functionality of the entire communicative system.

Targeting structures of intersubjectivity means to alter the communicative medium of systems subjects capable of acting and able to communicate on the basis

of their modular knowledge; to modulate the symbolic character of communication acts, and the communicative expression; to involve a tumor's living world and the modular knowledge of systems objects into the therapeutic calculus by implementing non-normative boundary conditions.

Targeting structures of normativity: The availability of normative systems structures in biological systems shows, that patterns of 'disparate' oncogenes and tumor suppressor genes may contribute to the constitution of different normative notions, to differential organizations of rationalizations, and modular arrangements of normative notions [62; Chap. 17)]. Targets are normative tumor structures (cell organelles, functional compartmentalisations, 'modules'), action norms (normative notions), and decision maxims (hubs and nodes). The assessment and appraisal of situational normative notions (for example, the hallmarks of cancer) is influenced by functional analytics (cellular secretome analytics, epigenetics, molecular imaging etc.) and the evaluation of perlocutionary processes, which may contribute to robustness.

Targeting structures of subjectivity ('to be an object in a biological system') means to alter the interpretation of a situation (i.e., nodes, hubs), the direction (orientation) of actions, the intention and motivation (instigation). Targeting structures of subjectivity may be realized, when the evolutionary systems status has been evaluated with appropriate technologies (Chap. 23).

Concurrent Evaluation of Evolutionary Processes in Different Normative Tumor Structures

Data derived from biomodulatory therapy approaches indicate that tumor-promoting rationalization processes are frequently preserved at the metastatic sites of an individual tumor disease, although cytogenetic heterogeneity of tumor cells is a common feature during clinical tumor progression [56; Chap. 23]. Evolutionary preservation of rationalization processes for maintaining distinct normative notions reveals that analyses of rationalizations constituting tumor-promoting normative notions play an important role to depict evolutionary processes, besides the traditional reductionist analyses (whole genome analytics; histopathology) (Chap. 15). The two perspectives open up methodologies enabling differential therapeutic access to metastatic tumor systems.

Obviously, the environment of metastatic organ sites defines restrictions and the scale, by which rationalizations are communicatively and contingently evolving, to sustain characteristic tumor-promoting normative notions (Chap. 16, 19). Evolving genomes in tumor cells are rather heterogeneous, but non-random—and considering this concrete restriction, we must assume that the arising chromosomal patterns are communicatively well organized to ensure the tumor cells' robustness and reproducibility. Non-randomness, evolutionary persistence and specific biomodulatory accessibility within an individual tumor disease is a frequently occurring feature of tumor-promoting rationalization processes, but—vice versa—redundant

background knowledge of cellular systems participators allows many ways to organize rationalization processes, just to constitute one single normative notion, like tumor-associated inflammation, angiogenesis, immune response etc. [3, 68; Chap. 2]. Compilation of these differential rationalization processes is the task of an evolution-adjusted tumor pathophysiology.

The hypothesis-triggered differential comprehension of evolutionary processes results in diversified, but equivalently applicable therapeutic approaches, i.e., the 'bottom-up' and the 'top-down' strategies (Chap. 22). These strategies have to be appropriately selected and adapted to the evolutionarily confined systems stage for achieving tumor control. In case of metastatic tumor diseases, it would seem the thing to use 'top-down' strategies to overcome cytogenetically based tumor heterogeneity (Chap. 2, 22).

Cellular Therapies In Situ

Cellular therapies in situ may be established by implementation of non-normative boundary conditions into the tumor's systems context and represent evolution-inducing therapies.

On the background of successfully administered biomodulatory therapy approaches, we propose that drivers of carcinogenesis (stress, noxa, chronic inflammation etc.) primarily induce adaptive changes via rationalizations and modularity. Redirection and modulation of the tissues' normativity is enabled by local or systemic modulation of tissue architectures and functions, which may be—as shown—consecutively digitalized as acquired (molecular-) genetic aberrations [18]. A full understanding of cancer biology and therapy through a cataloguing of the cancer genome is unlikely unless it is integrated into an evolutionary that means in a communicative context, explicated by an evolution theory. Tumor cell systems are getting evolved by the contemporarily restricted possibilities for redemption of external and internal modular knowledge by the respective systems objects. Aberrant tumor-associated genetic patterns are now pending to be reinterpreted on the background of modular and rationalization processes.

Hitherto existing perspectives favoring unity of patient care and contextualism are likely to consider qualitatively heterogeneous communicative actions, including modularly-designed tumor therapies, as too weak and presumably inefficacious. The reason for this view is that all hierarchies, that have developed by intentionally acquired knowledge (evolution historical considerations), are leveled to be discharged in a continuum of contingency programming, modularly-evolving systems features, and in continuous inter-systemic communicative exchange processes. On the other hand, the methodology of communicative therapeutic intervention (modular therapy) seems to be highly potent from a contextualist perspective. This view may be caused by the fact that incommensurable 'worlds', such as non-DNA-heritage and DNA heritage or different techniques for implementing modular knowledge and various modular tumor architectures, turn out to be pervious, despite their qualitatively

rather heterogeneous features [83]. Non-DNA-heritage and DNA heritage share a digitalized operative action pattern.

Adaptive Trial Design by Monitoring Changes in Normative Systems Structures (Systems Stage-Adapted Therapy)

Implementation of modular knowledge, rationalization processes and normative systems structures now enter the therapeutic calculus for establishing stepwise evolution-adjusted therapies and adaptive trial designs [83].

Biomodulation means to configure normative systems structures of tumors by the metronomic (e.g., continuous daily) implementation of non-normative boundary conditions, mostly via non-oncogene addicted targets, both in tumor and adjacent stroma cells. Implementation of modular knowledge facilitates to adaptively slow down the evolutionary growth promoting process of cancer, and not to unwisely accelerate evolution when applying classic cytotoxic drug therapy: 'Overtreatment' and long-term toxicity due to biological memory (epigenetic and genetic changes) may have an overall negative effect and can accelerate cancer evolution (secondary malignancy) following cytotoxic therapy.

Important questions yet still unanswered can be solved by an evolution theory:

- How can we use systems homeostasis to constrain cancer by modulating simultaneously multiple homeostasis systems in individuals?
- Is it possible to apply the evolutionary provided or therapeutically induced communication principle to slow down cancer progression?
- Can cancer be directed into a slow growth phase that will not trigger much heterogeneity? Evolution and therapeutically induced evolutionary processes drastically change the cooperative and competitive relationship between cancers and host. Cancer may be therapeutically directed to enter into a highly homogeneous phase, then constrained by therapeutically induced systems homeostasis mechanisms (Chap. 2, 19).

Drug Repurposing

Compared to conventional pulsed chemotherapy, biomodulatory therapy strategies are thought to be less susceptible to the development of drug resistance and to cause less toxicity [46]. Taking into account that the combinatorial use and repurposing of biomodulating agents might potentiate the antineoplastic effects without causing life threatening toxicities, targeting communicative expression of tumor systems objects (multi-dimensional rationalization processes) is judged to be a promising approach in tumor palliation. Drug repurposing research still remains a challenge for systems biological considerations [95].

Discussion

Dobzhansky wrote, "nothing in biology makes sense except in the light of evolution", and this, has not been sufficiently recognized yet by medicine [96]. Modular therapies exemplarily give indications of the 'metabolism' of evolutionary processes in tissues.

Three main factors emerged as our starting point for evolution theoretical considerations, an unmet medical need (systemically pretreated patients with metastatic tumors), a hypothesis-driven vision (the formal pragmatic communication theory) and technological advances to pursue that vision (biomodulatory therapy approaches, cellular gene transfection etc., clinical proteomics, epigenetics and molecular imaging techniques) (Fig. 12.8).

The present evolution theory on tumor development arises from a formal pragmatic communication theory and has been originated, starting from the three looming mainstays of acquiring new insights into novel therapy approaches assuming modular features (biomodulatory therapy) in diseased tissues, (1) the change from the classic conclusion logic (indicating a pathway responsible for cell death) to that of normative statements (how to control systems-associated processes with therapy modules to achieve response); (2) the change from object-associated to situation-associated systems interpretations (biomodulatory therapies in metastatic tumors); and (3) the change from an intentional (reductionist) to an evolution-based systems explanation (systems behavior and response) [68].

At this time, for situation-associated systems interpretations, we may use terms derived from theoretical considerations (evolution theory) on a tumor's modular systems architecture and on intercellular rationalization processes. The two methodological pillars (reductionist versus holistic) for creating tumor models complement each other in the same way as the benchmarks of communicative systems correspond to the components of which functional sequences are composed**.**

The proposed evolution theory on tumors aims at specification of novel therapy approaches of metastatic tumors (biomodulation, cellular therapy in situ) and at uncovering of modular systems structures (novel tumor pathophysiology). This approach is realized by a pragmatic communication-theoretical method for understanding communicatively linked systems objects, biochemical processes, and cell functions by communication-technical terms, namely the validity and denotation of systems objects.

The formal-pragmatic communication theory exceeds information theoretical approaches as well as the game theory, because normativity, modular features, subjectivity and intersubjectivity of systems objects are acknowledged beyond the simple exchange of information via communication lines or the reductionist assignment of functions.

Particularly, communication theory specifies the communication related prepositional circumstances, which are prerequisite to attribute particular systems objects

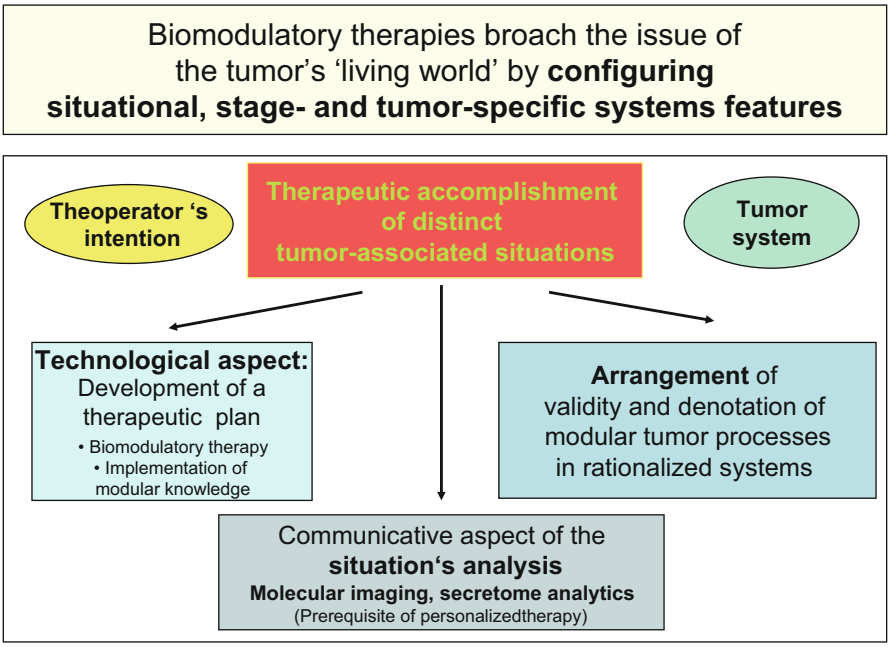

Fig. 12.8 Biomodulatory therapies broach the issue of the tumor's 'living world' as a holistic and therefore self-contained communication process by configuring situational, stage- and tumor-specific systems features. The tumor's **evolutionary-derived stages** are separated episodes of the tumor's 'living world' with respect to distinct issues or intentions, namely the aspired growth control of respective metastatic tumors

distinct communicative expression, and which define, whether a communicative expression is evolutionary conserved or whether the respective systems object is used in a novel communicative context (modular knowledge).

The theory is based on statements about retrospectively recognizable and scientifically accessible evolutionary processes, which contribute to a relief of function within a communicative modus, frequently, by enhancing complexity. In future probably other structures than the actually established cognitive-instrumental and practical structures are accessible for a reconstruction of evolutionary processes (Fig. 12.8). Our knowledge about communication processes is limited in so far as it is dependent on currently available communicative instruments and available evolution historical data.

What Does an Evolution Theory Accomplish?

A main task of an evolution theory will be to uncover more examples of rationalization processes constituting common normative notions of tumors, based on a very broad, but non- random pattern of acquired genetic aberrations. Multifaceted rationalization processes are utilized by respective tumor systems for constituting distinct

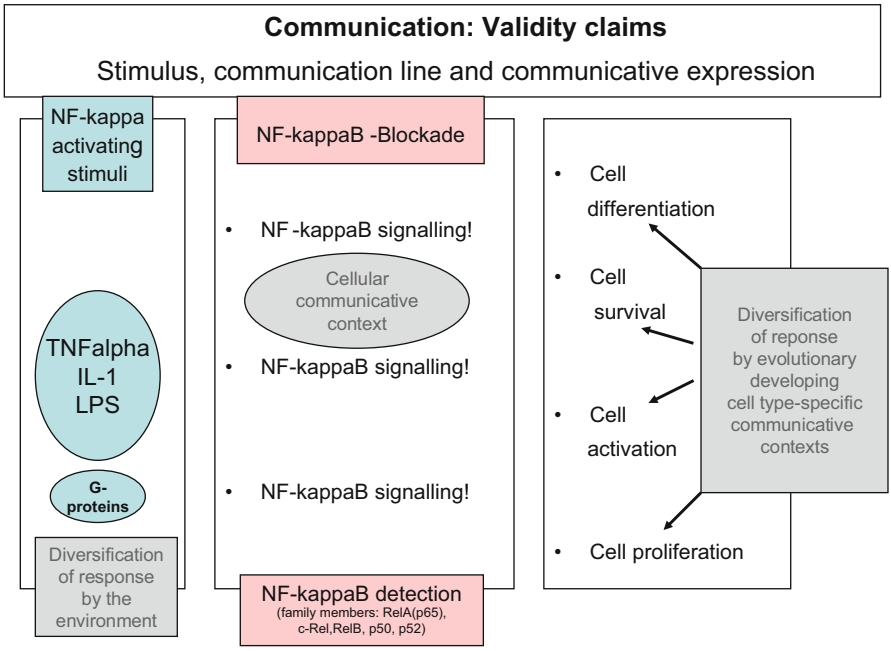

Fig. 12.9 The communicative expression of the activated NF-kappaB signalling pathway is modulated by extrinsic, environmental parameters and by intrinsic, evolutionary developing communicative contexts

tumor stages and tumor types and for supporting evolutionary confined normative systems structures, differential interfaces and correspondingly adaptive intersystemic exchange processes. The introduction of biomodulatory therapy regimens for treating metastatic tumors allows versatile involvement of clinical treatment strategies in communication- technically accessible novel tumor pathologies (evolution-adjusted tumor pathophysiology).

The implementation of therapies interfering with evolutionary tumor processes serves as

- A detector for therapeutic targets, which are derived from modular tumor architectures and rationalization processes. Biomodulatory therapies ('top-down' approaches) are "targeted" therapies using ubiquitously available targets, present on tumor and stroma cells, and aim at targeting holistic communicative structures (rationalization processes). The implementation of non-normative boundary conditions facilitates to redeem validity and denotation of specific systems objects within communicative tumor processes (Fig. 12.9).
- Therapy-relevant action-theoretical approaches may uncover the interwoven modular tumor architecture. This way, we can describe modular textures on a molecular

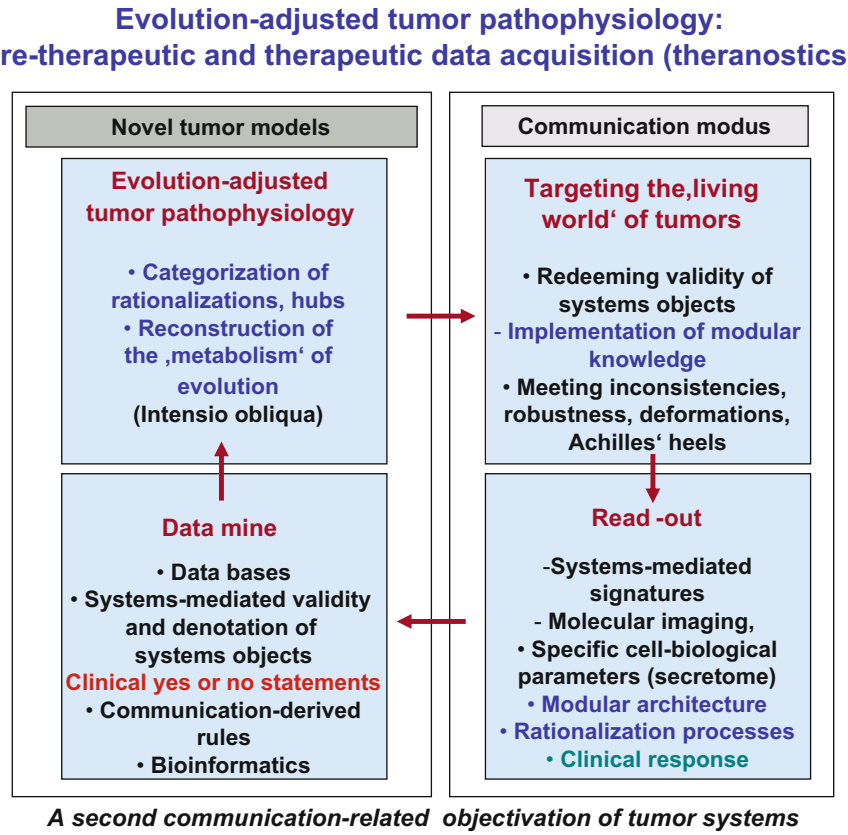

Fig. 12.10 Theme-dependent and closely interrelated areas of knowledge are the basis for reductionist approaches to uncover systems biology. According to reductionist systems interventions, scientists are observers of subject-object relations. However, if references of studied systems objects resolve during evolutionary tumor development, and systems objects are anticipating novel systems-related rationalization processes (e.g., differential integration of inflammation), then methodological considerations guided by 'intentio obliqua' are appropriate to reconstruct evolutionary systems stages (modular approach)

basis, (1) on the background of altered cell functions in the course of rationalization processes, and (2) with novel therapy-guiding 'universal' biomarkers (cellular secretome analytics) (Chap. 15).

In each new tumor case a few small regulatory changes may be detectable, sufficing to redeploy rationalization processes, which are robust, adaptable, and which create novel interfaces. By applying novel indirect methodologies ('intensio obliqua') for uncovering the architecture of rationalization processes, hubs within rationalization processes, or for identifying deformations and Achilles' heels in tumor systems, vulnerable nodal points of rationalization processes could be targeted in future with 'bottom-up' strategies (Fig. 12.10).

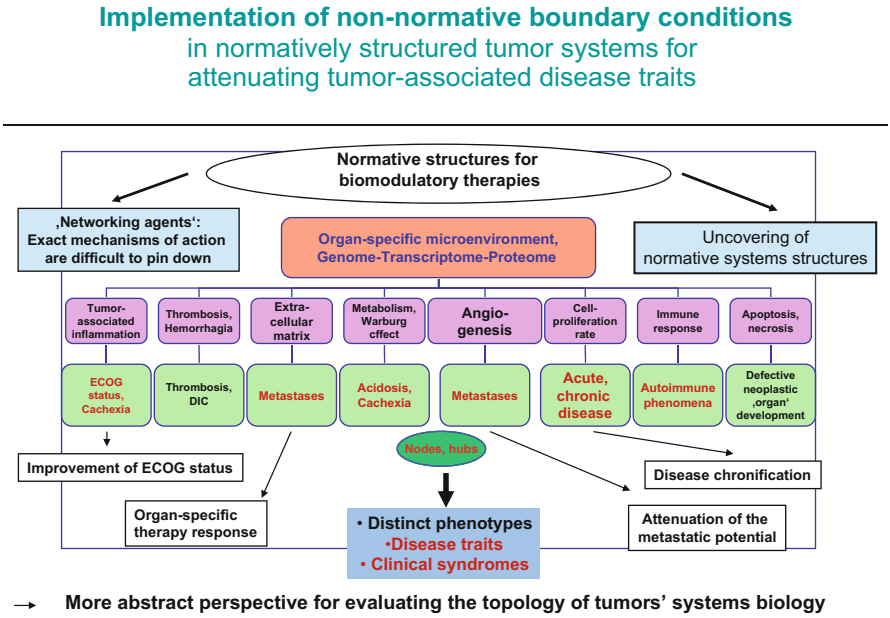

Fig. 12.11 Modular therapy approaches facilitate the detection of new networking interactions and the reconstruction of normative notions. Thereby, the context of discovery (modulation of tumor associated disease traits, biomarkers) has to be consistently separated from the context of justification (rational for a biomodulatory therapy approach). The currently established genomic/non-genomic biomodulatory therapies may lead to novel and more abstract perspectives for viewing the topology of tumor systems biology, inconsistencies, deformations, and Achilles' heels

Up to now, the success of cancer screening programmes solely depends on the assumption that small, primary tumors are curable if detected early enough. This field, however, could be further personalized by considering communication derived tumor pathophysiology, particularly rationalization processes (Chap. 15).

> An evolution theory allows a possible virtualization of the engagement to get experiences via implementation of non-normative boundary conditions (Pragmatic virtualization of communication acts)

Tumor models are based on normative systems structures; the 'metabolism' of evolution is linked to criticizable claims of validity and the redemption of validity and denotation on the background of a holistically acting communicative systems context; evolutionary conserved communicative structures may be newly defined by universal suppositions for a distinct communicative expression of a communication line or medium; the theoretical and technical instruments to evaluate the evolutionary and therapeutic impact of heritable/non-heritable evolutionary developments on the genetic and rationalization level, respectively, are now available (Fig. 12.8, 12.9, 12.10, 12.11, 12.12, 12.13, 12.14, 12.15).

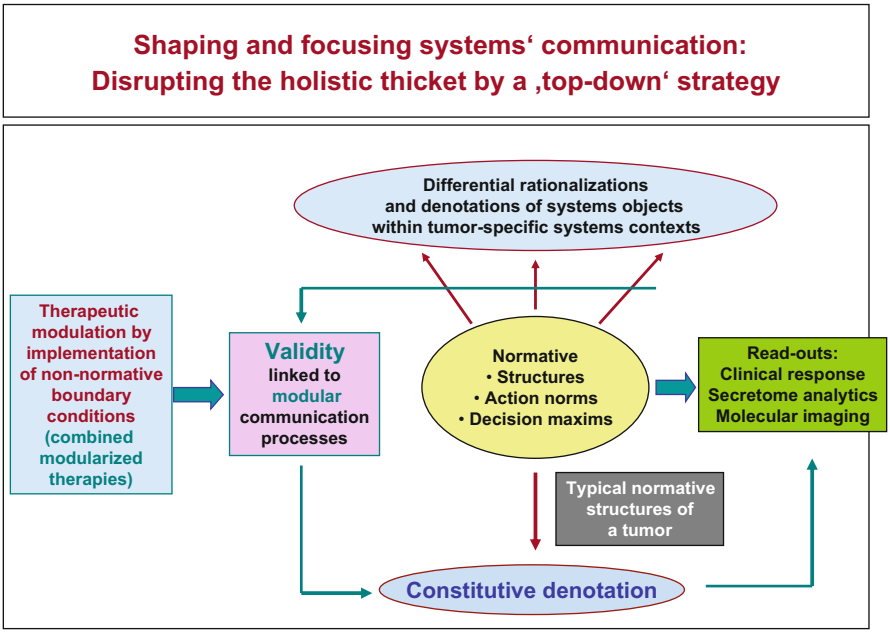

Fig. 12.12 Shaping and focusing systems' communication: disrupting the holistic thicket

The endogenous monitoring of time-related processes (**time-consciousness**) must be imminent in biological systems. Particularly, the operative interplay of functional and systems world could be a main cause for generating time-consciousness in biological systems (Chap. 11).

The newly established pragmatic communication-theoretical approach shows that causality in any particular form does not need to be a feature of every successful scientific explanation: Primarily the 'know that', the communicative rule accomplishing modular knowledge, which is mediated by the activity of biomodulatory therapy approaches is sufficient, whereas the 'know how' has to be further evaluated, again in a reductionist sense (Fig. 12.12). Introduction of communication derived rules may pragmatically resolve the problem of mutual causation of two phenomena [97].

A currently published 'evolution theory' proposes as evolutionary benchmarks some deeply grounded biological perspectives, i.e., 'natural selection acting on multicellular organisms to mold barriers and restraints, natural selection acting on infectious organisms to abrogate these protective mechanisms, and oncogenic selection which is responsible for the evolution of normal cells into cancerous cells' [98]: This way, biological systems disintegrate in the particularism of suggested relevant cuttings of the 'living world' in the sense of a neopragmatism.

An evolution theory allows a possible virtualization of the engagement to get (therapeutic) decisions via implementation of non-normative boundary conditions

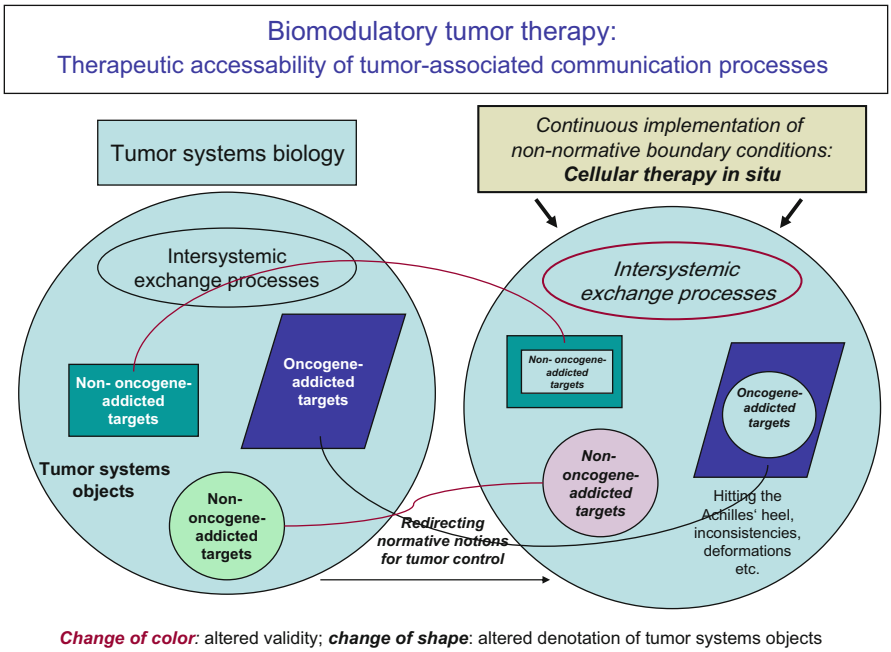

Fig. 12.13 In an evolutionary process, tumor and stroma cells may exploit the whole extent of evolutionary restricted rationalization features and tools of systems objects' modularity to implement the functional diversity of systems behavior aimed at promoting tumor growth, maintaining homeostasis and robustness towards perturbances. By therapeutic implementation of non-normative boundary conditions, rationalization processes and modular tools may be accessed for modulating normative notions of tumor systems (attenuation of tumor growth) via redemption of systems-constrained validity claims and consecutively systems objects' denotations

Biomodulatory therapy recommendations may be based on evolution theoretical considerations. The claim for objectivity on systems-biological processes studied via biomodulatory therapy approaches is based on a possible virtualization of the engagement to get experiences or decisions (Fig. 12.13). The virtualization is enabled by a discursive evaluation of hypothetical requirements for the validity of systems objects in a systems-biological model and hereby allows the generation of provable knowledge. These new methodological approaches for studying systems biology by a therapy-guided method may be an important supplementation of the established analytical/empirical studies on functional genomics in systems biology [50, 51, 68]. Therapies can be adapted (adaptive trial design) to situation-related and stage-dependent communicatively explicable evolutionary constraints by implementation of externally and internally derived modular knowledge.

Diversifying Palliative Care for Patients with Metastatic Cancer: Toxicity of therapy approaches and pharmaco-genomic aspects may be decisive in co-morbid or medically non-fit patients for decision-making. Communication-derived tumor

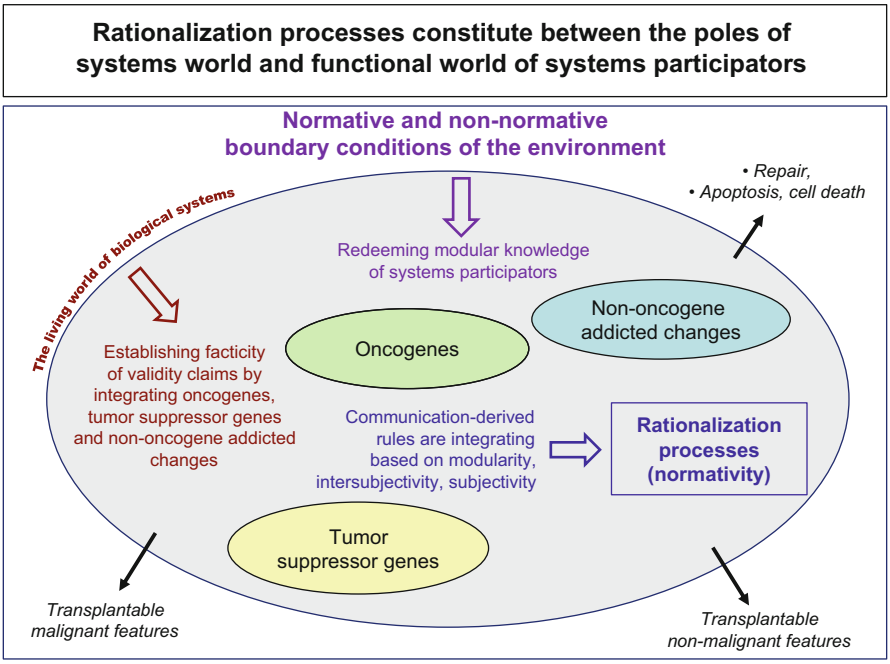

Fig. 12.14 Rationalization processes constitute between the poles of systems world and functional world of systems participators. Modulating determinants are the tumor's living world, normative as well as non-normative boundary conditions and the systems participators' modular knowledge. Rationalization processes are an attainment of tumor and stroma cells

pathophysiology will be a prerequisite for targeting multifaceted rationalizations of tumor-promoting normative notions (Fig. 12.14) (Chap. 19).

Personalizing Tumor Therapy by Novel Adaptive Trial Designs: By the possibility to virtualize the engagement to get situative experiences about tumor systems (communication-derived tumor pathophysiology) and decisions to tailor biomodulatory therapies, the possibility of an evolutionarily adapted modeling of cancer (cellular therapy in situ by adaptive therapies and novel adaptive trial designs) will continue to increase our understanding of tumor pathophysiology and may contribute to an evolution-oriented design of systems biological strategies. Adaptive trial designs aim at diagnosing and clinically managing tumor diseases on a novel personalized level (theranostics). Basic science is getting directly involved in the reconstructive process, even though an approach has been established directed from bedside to bench aiming at implementing clinical practical care (adaptive trial designs) as scientific object in patient care (Fig. 12.15).

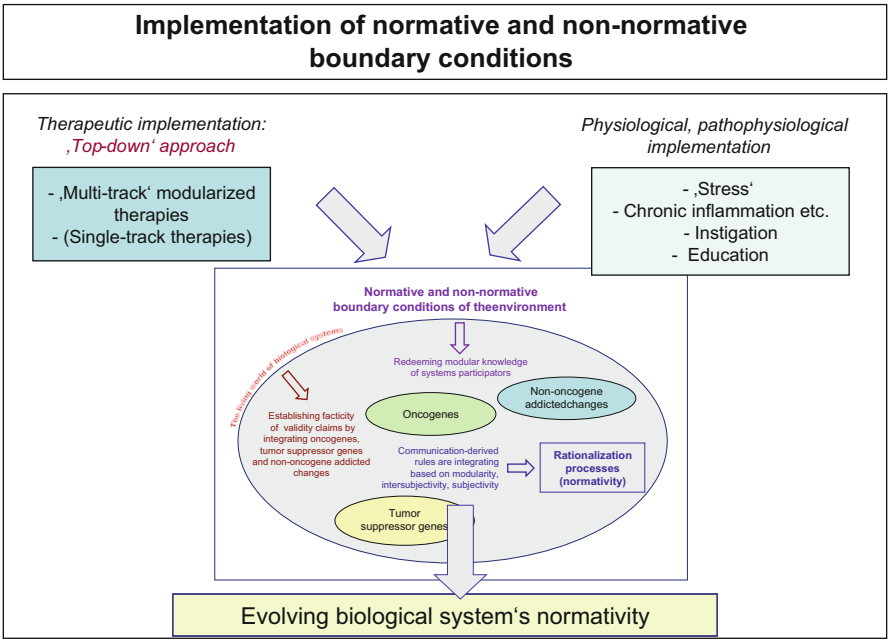

Fig. 12.15 Implementation of normative or non-normative boundary conditions to redirect and modulate biological systems' normativity: 'Top-down' strategies concertedly target rationalizations of tumor-promoting normative notions. 'Bottom-up' approaches aim at targeting single tumor growth promoting communication lines. Both approaches have in common that their efficacy is based on the redirection and modulation of rationalization processes (Chap. 22)

References

1. Vineis P, Berwick M (2006) The population dynamics of cancer: a Darwinian perspective. Int J Epidemiol 35:1151–1159
2. Heng HH, Stevens JB, Bremer SW, Liu G, Abdallah BY, Ye CJ (2011) Evolutionary mechanisms and diversity in cancer. Adv Cancer Res 112:217–253
3. 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 5:232–242
4. Beerenwinkel N, Antal T, Dingli D et al (2007) Genetic progression and the waiting time to cancer. PLoS Comput Biol 3:e225
5. Gerhart J, Kirschner M (2007) The theory of facilitated variation. Proc Natl Acad Sci USA 104(Suppl 1):8582–8589
6. Cairns J (1979) Mutation selection and the natural history of cancer. Nature 255(5505):197–200
7. Nowell PC (1976) The clonal evolution of tumor cell populations. Science 194(4260):23–28
8. Crespi B, Summers K (2005) Evolutionary biology of cancer. Trends Ecol Evol 20:545–552
9. Merlo LM, Pepper JW, Reid BJ, Maley CC (2006) Cancer as an evolutionary and ecological process. Nat Rev Cancer 6:924–935
10. Nowak MA (2006) Five rules for the evolution of cooperation. Science 314:1560–1563
11. Garcia-Mata R, Boulter E, Burridge K (2001) The 'invisible hand': regulation of RHO GTPases by RHOGDIs. Nat Rev Mol Cell Biol 12:493–504
12. Gatenby RA, Vincent TL (2003) An evolutionary model of carcinogenesis. Cancer Res 63:6212–6220

13. Grouchy J (1977) Theodore Boveri and the chromosomal theory of oncogenesis. Nouv Rev Fr Hematol Blood Cells 18:1–4
14. Axelrod R, Axelrod DE, Pienta KJ (2006) Evolution of cooperation among tumor cells. Proc Natl Acad Sci USA 103:13474–13479
15. Ye CJ, Stevens JB, Liu G et al (2009) Genome based cell population heterogeneity promotes tumorigenicity: the evolutionary mechanism of cancer. J Cell Physiol 219:288–300
16. Pavlicev M, Cheverud JM, Wagner GP (2011) Evolution of adaptive phenotypic variation patterns by direct selection for evolvability. Proc Biol Sci 278:1903–1912
17. Attolini CS, Michor F (2009) Evolutionary theory of cancer. Ann N Y Acad Sci 1168:23–51
18. Lin C, Yang L, Tanasa B et al (2009) Nuclear receptor-induced chromosomal proximity and DNA breaks underlie specific translocations in cancer. Cell 139:1069–1083
19. Knudson AG, Jr (1971) Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA 68:820–82
20. Armitage P, Doll R (2004) The age distribution of cancer and a multi-stage theory of carcinogenesis. Int J Epidemiol 33:1174–1179
21. Radisky DC, Levy DD, Littlepage LE et al (2005) Rac1b and reactive oxygen species mediate MMP-3-induced EMT and genomic instability. Nature 436:123–127
22. Lacoste S, Wiechec E, Dos Santos Silva AG et al (2010) Chromosomal rearrangements after ex vivo Epstein-Barr virus (EBV) infection of human B cells. Oncogene 29:503–515
23. 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 220:538–547
24. Louhelainen J, Szyfter K, Szyfter W, Hemminki K (1997) Loss of heterozygosity and microsatellite instability in larynx cancer. Int J Oncol 10:247–252
25. Green MR (2008) Senescence: not just for tumor suppression. Cell 134:562–564
26. Merlo LM, Maley CC (2010) The role of genetic diversity in cancer. J Clin Invest(120):401–403
27. Jablonka E, Lamb M (2002) Creating bridges or rifts? Developmental systems theory and evolutionary developmental biology Bioessays 24:290–291
28. Nicholson MJ, Duesberg P (2009) On the karyotypic origin and evolution of cancer cells. Cancer Genet Cytogenet 194:96–110
29. Desper R, Gascuel O (2004) Theoretical foundation of the balanced minimum evolution method of phylogenetic inference and its relationship to weighted least-squares tree fitting. Mol Biol Evol 21:587–598
30. Shibata D, Tavare S (2006) Counting divisions in a human somatic cell tree: how, what and why? Cell Cycle 5:610–614
31. Kim Y (2007) Rate of adaptive peak shifts with partial genetic robustness. Evolution Int J org Evolution 61:1847–1856
32. Lee HO, Silva AS, Concilio S et al (2011) Evolution of tumor invasiveness: the adaptive tumor microenvironment landscape model. Cancer Res 71:6327–6337
33. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144:646–674
34. Greaves M (2009) Darwin and evolutionary tales in leukemia. The Ham-Wasserman Lecture. Hematology Am Soc Hematol Educ Program 3–12
35. Heng HH (2009) The genome-centric concept: resynthesis of evolutionary theory. Bioessays 31:512–525
36. Califano A (2011) Rewiring makes the difference. Mol Syst Biol 7:463
37. Goh AM, Coffill CR, Lane DP (2011) The role of mutant p53 in human cancer. J Pathol 223:116–126
38. 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. Springer, pp 3–7. doi:10.1007/978–90-481–9531-2_1
39. Reichle A, Hildebrandt GC (2009) Principles of modular tumor therapy. Cancer Microenviron 2(Suppl 1):227–237
40. Ravandi F, Cortes JE, Jones D et al (2010) Phase I/II study of combination therapy with sorafenib, idarubicin, and cytarabine in younger patients with acute myeloid leukemia. J Clin Oncol 28:1856–1862

41. Metzelder S, Wang Y, Wollmer E et al (2009) Compassionate use of sorafenib in FLT3-ITD-positive acute myeloid leukemia: sustained regression before and after allogeneic stem cell transplantation. Blood 113:6567–6571
42. Mahon FX, Rea D, Guilhot J et al (2010) Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol 11:1029–1035
43. Falchi L, Rege-Cambrin G, Fava C et al (2010) Sustained molecular remissions are achievable with tyrosine kinase inhibitor therapy in patients with chronic myeloid leukemia and additional cytogenetic clonal evolution. Cancer Genet Cytogenet 199:139–142
44. Schrattenholz A, Groebe K, Soskic V (2010) Systems biology approaches and tools for analysis of interactomes and multi-target drugs. Methods Mol Biol 662:29–58
45. Gerber DE, Minna JD (2010) ALK inhibition for non-small cell lung cancer: from discovery to therapy in record time. Cancer Cell 18:548–551
46. Reichle A, Hildebrandt GC (2008) Systems biology: a therapeutic target for tumor therapy. Cancer Microenviron 1:159–170
47. 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
48. 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, pp 243–262. doi:10.1007/978–90-481–9531-2_11
49. Beck IME, Haegemann G, de Bosscher K (2010) Molecular cross-talk between nuclear receptors and nuclear factor-NFkappaB. In: From molecular to modular tumor therapy: the tumor microenvironment, vol 3, part 3. Springer, pp 191–242. doi:10.1007/978–90-481–9531-2_10
50. Pitteri SJ, Kelly-Spratt KS, Gurley KE et al (2011) Tumor microenvironment-derived proteins dominate the plasma proteome response during breast cancer induction and progression. Cancer Res 71:5090–5100
51. Lam LL, Emberly E, Fraser HB, Neumann SM, Chen E, Miller GE, Kobor MS (2012) Factors underlying variable DNA methylation in a human community cohort. Proc Natl Acad Sci USA 109(Suppl 2):17253–60. doi: 10.1073/pnas.1121249109. Epub 2012 Oct 8
52. 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
53. Reichle A, Hildebrandt GC (2010) From molecular to modular, from theme-dependent to evolution-adjusted tumor therapy. In: From molecular to modular tumor therapy. the tumor microenvironment, vol 3, part 7. Springer, pp 467–489. doi:10.1007/978–90-481-9531-2_27. 223
54. Paget S (1989) The distribution of secondary growths in cancer of the breast. 1889. Cancer Metastasis Rev 8:98–101
55. Chen LL, Blumm N, Christakis NA, Barabasi AL, Deisboeck TS (2009) Cancer metastasis networks and the prediction of progression patterns. Br J Cancer 101:749–758
56. Coghlin C, Murray GI (2010) Current and emerging concepts in tumour metastasis. J Pathol 222:1–15
57. Kaplan RN, Riba RD, Zacharoulis S et al (2005) VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. Nature 438:820–827
58. Raaijmakers MH, Mukherjee S, Guo S et al (2010) Bone progenitor dysfunction induces myelodysplasia and secondary leukaemia. Nature 464:852–857
59. Shackleton M, Quintana E, Fearon ER, Morrison SJ (2009) Heterogeneity in cancer: cancer stem cells versus clonal evolution. Cell 138:822–829
60. Zipori D (2004) The nature of stem cells: state rather than entity. Nat Rev Genet 5:873–878
61. Gatenby RA, Gillies RJ, Brown JS (2011) Of cancer and cave fish. Nat Rev Cancer 11:237–238

62. Kvinlaug BT, Chan WI, Bullinger L et al (2011) Common and overlapping oncogenic pathways contribute to the evolution of acute myeloid leukemias. Cancer Res 71:4117–4129
63. Sottoriva A, Vermeulen L, Tavare S (2011) Modeling evolutionary dynamics of epigenetic mutations in hierarchically organized tumors. PLoS Comput Biol 7:e1001132
64. Rubin H (2009) Saturation density of skin fibroblasts as a quantitative screen for human cancer susceptibility. Cancer Epidemiol Biomarkers Prev 18:2366–2372
65. Michor F, Nowak MA, Iwasa Y (2006) Evolution of resistance to cancer therapy. Curr Pharm Des 12:261–271
66. Reichle A, Hildebrandt GC (2010) To be an object in a biological system: the necessity of a formal-pragmatic communication theory. In: From molecular to modular tumor therapy: the tumor microenvironment, vol 3, part 9. Springer, pp 537–544. doi:10.1007/978–90-481–9531-2_26
67. Dingli D, Chalub FA, Santos FC, Van SS, Pacheco JM (2009) Cancer phenotype as the outcome of an evolutionary game between normal and malignant cells. Br J Cancer 101:1130–1136
68. 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:10.1007/978–90-481–9531-9532
69. 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
70. Reichle A, Hildebrandt GC (2010) Uncovering tumor systems biology by biomodulatory therapy strategies. 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
71. Wagner GP, Pavlicev M, Cheverud JM (2007) The road to modularity. Nat Rev Genet 8:921–931
72. Hartwell LH, Hopfield JJ, Leibler S, Murray AW (1999) From molecular to modular cell biology. Nature 402:C47–C52
73. Heinz S, Benner C, Spann N et al (2010) Simple combinations of lineage-determining transcription factors prime cis-regulatory elements required for macrophage and B cell identities. Mol Cell 38:576–589
74. Weber BN, Chi AW, Chavez A et al (2011) A critical role for TCF-1 in T-lineage specification and differentiation. Nature 476:63–68
75. Puglisi R, Maccari I, Pipolo S et al (2012) 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 227:1420–1427
76. Spemann H, Mangold H (2001) Induction of embryonic primordia by implantation of organizers from a different species. 1923. Int J Dev Biol(45):13–38
77. Kar G, Gursoy A, Keskin O (2009) Human cancer protein-protein interaction network: a structural perspective. PLoS Comput Biol 5:e1000601
78. Kitano H (2003) Cancer robustness: tumour tactics. Nature 426:123
79. Feret J, Danos V, Krivine J, Harmer R, Fontana W (2009) Internal coarse-graining of molecular systems. Proc Natl Acad Sci USA 106:6453–6458
80. Harmer R, Danos V, Feret J, Krivine J, Fontana W (2010) Intrinsic information carriers in combinatorial dynamical systems. Chaos 20:037108
81. Grauer O, Hau P (2010) Could be systems-directed therapy approaches promising in glioblastoma patients? In: From molecular to modular tumor therapy: the tumor microenvironment, vol 3, part 2. Springer, pp 133–157. doi:10.1007/978–90-481–9531-2_8
82. Wagner GP, Kenney-Hunt JP, Pavlicev M, Peck JR, Waxman D, Cheverud JM (2008) Pleiotropic scaling of gene effects and the cost of complexity. Nature 452:470–472
83. Reichle A, Vogt T, Hildebrandt GC (2010) A methodological approach to personalized therapies in metastatic cancer. In: Reichle A, (ed) from molecular to modular tumor therapy: the tumor microenvironment, vol 3, part 8. Springer, pp 507–33. doi:10.1007/978–90-481-9531-2_25
84. Trosko JE, Chang CC (1978) Environmental carcinogenesis: an integrative model. Q Rev Biol(53):115–141

85. Vineis P, Xun W (2009) The emerging epidemic of environmental cancers in developing countries. Ann Oncol 20:205–212
86. Lefevre S, Knedla A, Tennie C et al (2009) Synovial fibroblasts spread rheumatoid arthritis to unaffected joints. Nat Med 15:1414–1420
87. Rodig SJ, Ouyang J, Juszczynski P et al (2008) AP1-dependent galectin-1 expression delineates classical hodgkin and anaplastic large cell lymphomas from other lymphoid malignancies with shared molecular features. Clin Cancer Res 14:3338–3344
88. Bacac M, Provero P, Mayran N, Stehle JC, Fusco C, Stamenkovic I (2006) A mouse stromal response to tumor invasion predicts prostate and breast cancer patient survival. PLoS One 1:e32
89. 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 303:1960–1964
90. Chabner BA, Roberts TG Jr (2005) Timeline: Chemotherapy and the war on cancer. Nat Rev Cancer 5:65–72
91. Markert CL (1968) Neoplasia: a disease of cell differentiation. Cancer Res 28:1908–1914
92. Hagemann T, Lawrence T, McNeish I et al (2008) "Re-educating" tumor-associated macrophages by targeting NF-kappaB. J Exp Med 205:1261–1268
93. Vogelstein B, Fearon ER, Hamilton SR et al (1988) Genetic alterations during colorectal-tumor development. N Engl J Med 319:525–532
94. Chu D (2011) Complexity: against systems. Theory Biosci 130:229–245
95. Oprea TI, Bauman JE, Bologa CG et al (2011) Drug Repurposing from an Academic Perspective. Drug Discov Today Ther Strateg 8:61–69
96. Dobzhansky T (1973) Nothing in biology makes sense except in the light of evolution. The American Biology Teacher 35:125–129. http://www.2think.org/dobzhansky.shtml
97. Chindelevitch L, Ziemek D, Enayetallah A, Randhawa R, Sidders B, Brockel C, Huang ES (2012) Causal reasoning on biological networks: interpreting transcriptional changes. Bioinformatics 28(8):1114–1121
98. Ewald PW, Swain Ewald HA (2013) Toward a general evolutionary theory of oncogenesis. Evol Appl 6(1):70–81