Chapter 11
Criticizable Claims for the Validity of Communication Acts in Biological Systems: Therapeutic Implications in Cancer

Albrecht Reichle, Christopher Gerner and Guy Haegeman

Abstract Basis for the comprehension of biological systems are experimentally, and in the case of metastatic tumors also therapeutically derived data, mirroring the context-dependent validity of communicatively integrated systems objects (molecules, pathways, cells etc.). Validity claims of experimentally defined references in terms of systems objects seem to be routinely transferable into arbitrary evolving systems. This transfer is irrespective of the self-evident assumption that novel systems functions may spin off and that those tumors show novel compositions of acquired chromosomal and molecular-genetic aberrations. We are used to transfer references of experimentally defined systems objects into novel situation-embossed systems contexts, even though such experimentally-derived references are inevitably situation-linked and always attributable only ex post, particularly in case of evolving biologic systems. The present paper aims at reconstructing communication-derived rules and at showing how validity claims, which inevitably adhere to objects in biological systems, may be uncovered and therapeutically utilized. Hypothesis-driven tumor models may serve as challenge to reinterpret the myriad of available biological data in a communicative context. The main task remains to reconstruct observable communicative interactions on the expressive level and to select and extend methodologies, which have the capacity to monitor functional changes of cell systems in response to (therapeutic) perturbations.

A. Reichle (✉)
Department of Hematology and Oncology,
University Hospital Regensburg,
93052 Regensburg, Germany
e-mail: albrecht.reichle@ukr.de

C. Gerner
Institut für Analytische Chemie Universität Wien,
Währinger Straße 38,
A-1090 Wien, Germany

G. Haegeman
Laboratory of Eukaryotic Gene Expression and Signal Transduction (LEGEST),
Department of Physiology, Ghent University,
K.L. Ledeganckstraat 35, Gent, Belgium

A. Reichle (ed.), *Evolution-adjusted Tumor Pathophysiology,*
DOI 10.1007/978-94-007-6866-6_11,

Introduction

Cancer is a leading cause of death worldwide, particularly in Western countries [1] and, in most tumor types, early diagnosis of localized tumors offers the best chance for cure. In metastatic tumor stages, the efficacy of currently available therapy approaches is still dissatisfying. However, most cancer patients suffer from advanced or metastatic tumor disease at initial diagnosis. Targeted therapy approaches have significantly improved outcome in molecularly defined tumor subgroups.

Therapeutic success in selected tumor entities with molecular-directed therapies has fostered the discussion about personalized tumor therapy on a rational basis [2], resulting in a persistent demand for personalized tumor therapy. Over time however, its realization proved to be more difficult than expected. The implementation of molecularly targeted therapies is continuously stipulated, but we are still far removed from our subject in the clinical setting [3–5]. Therefore, we should also think about methodological concerns as one reason for the delayed progress in personalizing tumor therapy.

For many diseases, such as metastatic tumors, that have undergone empty 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. The focus should be on an individual's evolution-linked tumor phenotype rather than only on molecular and theme-dependent knowledge [6].

The necessity of developing novel methodological approaches to bridge theory and therapeutic practice may be exemplarily highlighted by common observations revealing discrepancies between theory and practice [7, 8]. Phrasing obstacles for translational research in the clinical field allows focusing on issues that have to be covered by novel hypothesis-triggered methodologies, for instance, the reconstruction of communicative relations of systems objects (pathways, molecules, cells, etc.) within a tumor system on the basis of a formal pragmatic communication theory.

- Not every **clinical trial** has to re-confirm the non-transferability of reductionist, context-dependent knowledge (derived from basic science) on completely novel evolution-based contexts in metastatic tumor systems. Systems objects and communication lines as the benchmarks of communication may have striking common features in a preclinically-derived systems context as well as in a novelly evolving systems context: An identical therapy-relevant systems object may be ascertained with respective methods, both, in the 'historical' control and in the novelly evolving tumor system, including all its variations, up- or down-regulations, or molecular modifications. But targeting the specific molecule with the respective scheduled 'targeted' drug or drug combination may lead to differential or completely different results [9, 10]: Multi-facetted chromosomal or molecular-genetic aberrations, particularly in tumor cells but also in stroma cells, may ultimately determine the communicative expression, i.e., the meaning of systems objects in a therapeutically relevant way (Chap. 7).

- **Nonlinear responses** of differentially developed tumor systems are a well-known phenomenon: Philadelphia positive chronic myelocytic leukemia may be live-long controlled in more than 60 % of patients by inhibition of chimeric tyrosine kinase [11]. Additional aberrations in CML disease cause many problems with regard to disease control by respective targeted therapies [12]. Sorafenib, another tyrosine kinase inhibitor, is weakly active in combination with chemotherapy in Flt-3 positive acute myelocytic leukemia. However, administered as a single drug, it may induce continuous complete remission in patients with Flt-3 positive relapse after allogeneic stem cell transplantation [9, 10]: Seemingly minor therapeutically induced perturbations of tumor systems may contribute to rapid and massive changes in response dependent on the kinases' communicative systems context (Chap. 7).
- **High-throughput array data** or in silico approaches contribute to a minor degree to novel modes of therapy action, for instance, combined targeted therapies [3], and innovative drug designs, such as in chronic myelocytic leukemia or ALK-positive adeno-carcinomas of the lung [11, 13]. To overcome this gap it is necessary to process quantitative proteomic data from appropriate hypothesis-driven models, for instance, based on the communicative reconstruction of tumor-immanent normative functions [3, 14–17].
- **Natural drugs** derived from plants (ethno-pharmacology) give decisive hints on the modular nature of mechanisms of action, particularly in comparison with physiological compounds [17, 18]. Furthermore, these compounds show how normative notions within tumor systems, for instance, maintenance of proinflammatory and proangiogenic processes during tumor progression, are differentially rationalized within various tumor systems [19–21]. Therefore, tumors may recourse on completely different communication lines to constitute normative notions within tumor systems, which are—vice versa—perceived as unique by clinical observers. These normative notions are tightened to a few, seemingly characteristic, markers, symbolizing distinct normative notions (inflammation, angiogenesis, etc.) [22–25; Chap. 17].
- **Validity claims** of experimentally defined references in terms of systems objects seem to be routinely transferable into arbitrary evolving systems. This transfer is irrespective of the self-evident assumption that novel systems functions may spin off and that those tumors show novel compositions of acquired chromosomal and molecular-genetic aberrations. We are used to transfer references of experimentally defined systems objects into novel situative systems contexts (that represent a distinctive evolution-derived phenomenological status), even though such experimentally-derived references are inevitably situative and always attributable only ex post, particularly in case of evolving biologic systems [26]. The present paper aims at reconstructing communication-derived rules and at showing how validity claims, which inevitably adhere to objects in biological systems, may be uncovered and therapeutically utilized.

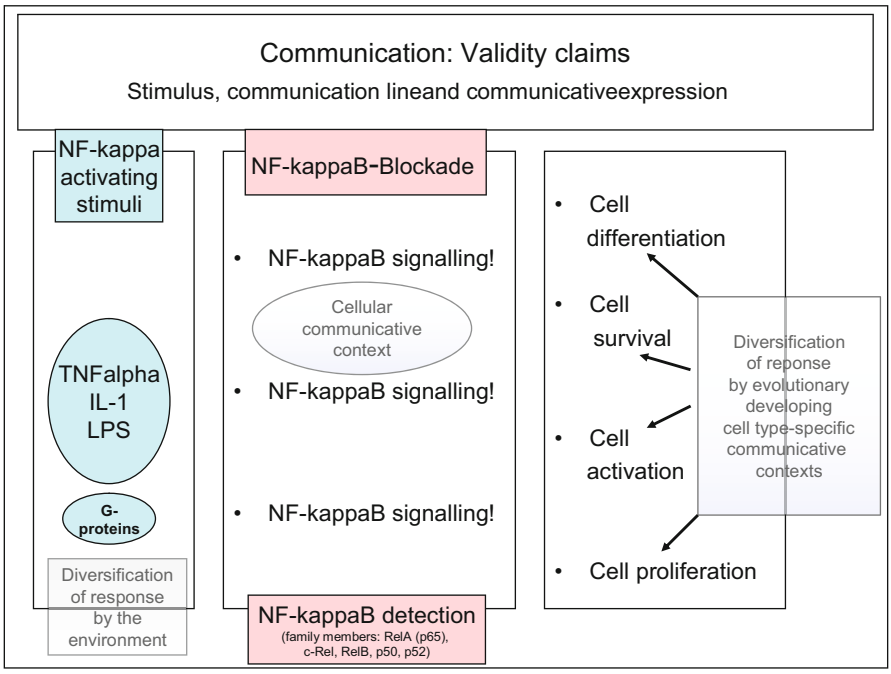

Fig. 11.1 The communicative expression of the activated NF-kappaB signalling pathway is modulated by extrinsic, environmental parameters and by intrinsic, evolutionary developing communicative contexts

Perception of Validity

A significant difference exists between a communication medium (ion channels, molecular pathways, signaling integrators, etc.) or communication lines (gap junctions, signaling pathways, nerves, etc.) and the underlying communicative expression (purpose). Communication mediums (cytokines, hormones, etc.) 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. 11.1).

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.

Pragmatic Functions of Communicative Expression

By its activation, a communication line is placed (1) in relation to its external reality, the microenvironment, and corresponding to the modus, how the external reality may be experienced (e.g., controlling circuits, sensory systems, modular knowledge, etc.). Furthermore, a communication line is related to the (2) internal reality corresponding to the mode of rationalization of the tumor's living world (defined as the tumor's holistic communicative world). Further relations are the (3) intersubjective reality that corresponds to what a communicative systems participator may express as its intention, and (4) the normative structure, i.e., how it is recognized by a socially linked cellular system (normative functions, i.e., inflammation, angiogenesis, etc.) [27–29].

After the activation of a communication line, the respective communicative expression should be assessed. Communicative expression has three pragmatic functions, namely to represent something, to express an intention, and to establish an intersubjective relationship of systems objects.

During the activation procedure, communicative expression is subjected to validity claims. As a non-situated communication line or as a purely communication-technical formation, communicative expression cannot fulfill these claims because of attributed and historically objectified references, which may be quantitatively and qualitatively appreciated.

Prepositions of Validity

Comprehensibility is a universal claim that can be raised by communicative participators with regard to communication lines as well as a prerequisite for the correct function of communication tools. The validity of a stated proposition depends on whether the proposition represents a fact or an experience. The validity of an expressed intention depends on whether it corresponds to what is actually intended by the initiator of a communication process. The validity of a performed communication act depends on whether this action conforms to a recognized normative background. A communication line aims at comprehensibility, whereas a successful communicative expression must satisfy additional validity claims: It must be ascertainable for systems objects as something that is represented in the living world; additionally, communicative expressions account as right (no fallacy!) insofar as it conforms to recognized expectations of a cell society.

Modules and Modular Knowledge

We commonly proceed on the assumption that a proven systems object complies with a distinct function or has a particular meaning. We are less likely to suggest that primarily insufficiently comprehended tumor systems with multiple and varying

chromosomal or molecular-genetic aberrations may assign distinct systems objects with novel and probably contradictory meanings as suggested by preclinical data [30].

We cannot continue to describe proteins, pathways, and cell interactions on a solely physical-chemical level and by usual chemical kinetics [31, 32]. On the one hand, mathematical realization of the entire combinatorics of all possible interactions and variations of systems objects is hardly possible; on the other hand, many systems objects are known to adopt surprising functions depending on their communicative context [9, 10]. These functions may be poorly delineated from the physical-chemical behavior of systems objects themselves and are obviously derived from communication-associated rules [31, 32], which mirror validity claims. The communication-derived, context-dependent tool of possibilities for adopting novel systems functions via modular rearrangements is termed the modular knowledge of a systems object. Systems objects are intrinsic information carriers in combinatorial dynamical systems, which are characterized by situatively arising modules and rationalizations of normative notions [14, 27, 32].

Modularity (Object-Subject Relation)

The increasingly higher organization of a tumor cell system during tumor growth results in the development of systems perspectives, in which the functional 'world' of distinct cell types is featured as a component of the respective systems 'world' [14, 33–35]. In the present context, modularity is a formal pragmatic communicative systems concept, describing the degree and specificity to which systems objects (cells, pathways, molecules, e.g., transcription factors, etc.) may be communicatively separated in a virtual continuum, reassembled, and rededicated (e.g., co-option) to alter the validity and denotation of communication processes. This concept refers to possible interactions between the systems objects in a tumor as well to the degree to which the communicative rules of the systems architecture (for establishing validity and denotation) enable or prohibit the focus on validity and denotation. Systems objects acquire the features of symbols, which are rich in content and able to acquire novel references by rearranging validity and, consecutively, denotation. Tumors consist of modules, which become a scientific object by uncovering a tumor's living world with biomodulatory and therefore modularly designed events. A formal-pragmatic theory about the denotation of a communication process may establish an internal interrelation of denotation and validity [14].

Formal Pragmatic Theory of Meaning

The formal pragmatic theory of meaning originates from the simple consideration that a systems participator only 'understands' a communication act, if it perceives the conditions that make it acceptable.

At issue are objective conditions of validity that may be (therapeutically) inferred directly from the communicative content of a respective communication-technical expression used. This validity claim rests on a reservoir of potential reasons with which it can redeem, if necessary.

The available reasons interpret the validity conditions that are part of the conditions that render validity claims worthy of intersubjective recognition and make a corresponding communication expression acceptable. Correspondingly, identical biomodulatory therapies may exert differential effects dependent on the differentially embossed validity conditions in situative evolutionary processes [36].

Only an additional evaluation step makes it possible to turn from the exclusive consideration of formal communication techniques (signaling pathways, etc.) to therapy-relevant communication pragmatics, which assess the conditions of communication for reaching understanding (physiological or pathophysiological status) or strategic (therapeutic) communicative interventions. A prerequisite for the additionally introduced evaluation step is the revision of basic ontological and mostly reductionist-based concepts established in biology.

- An exact **formal pragmatic analysis** of a successful communication act is necessary (i.e., cellular secretome analytics, molecular imaging) because, in communicative actions, the structure of the use of communication tools aimed at reaching understanding is inherently linked with teleological structures of action (normative notions).
- **Rationalization and robustness:** 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 [27, 37]. The implementation of a new form of integration (rationalization) of these 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 cell systems may recourse on differential rationalization processes (perlocutionary act in linguistics), which is symbolized by rather different communication lines and systems objects to maintain normative notions (robustness).
- **Systems actors are subjected to constrains**, which again restrict them to adapt attitudes facilitating distinct normative notions with respective communication lines. From a therapeutic point of view, it is important that attitudes for communicative actions are obviously more loaded with presuppositions (an indication of robustness) than the objectifying attitudes of strategic actors ('knowing that'), i.e., physicians administering a therapy, which interferes with the holistic communicative tumor system (biomodulatory therapy). On the other hand, communicative interactions mediated through acts for reaching understanding exhibit a multi-facetted but more restricted structure than strategically intended actions.
- **The frequently applied game theory as well as the theory of scale relativity** decisively restrict an action-oriented theory towards the reaching of understanding in so far that these theories neglect the dynamics of reciprocally (by the systems

objects) intended criticizable validity claims [38, 39]. However, criticizable validity claims are essential for communicative action. Insofar, game theory underlies a presupposed validity consensus, which must not necessarily be present in evolving tumor systems. Game theory approaches may be considered useful for the simplification of complex sets of non-equilibrium conditions by the introduction of 'multi-target drug design games' [38]. Multimodal interactions may also provide an opportunity to induce evolutionary (also epigenetically driven) processes and novel intersystemic exchanges so that the use of game theory seems to be restricted for assessing evolution-adjusted references of systems objects.

- **Vagueness about the communicative expression:** Communicative actions coordinating factually raised and recognized validity claims result in unconditionality, rules entering the everyday intermolecular and intercellular communicative practice. Simultaneously, vagueness arises about the communicative expression of a communication line within a novel systems context. The communicatively subjected systems participators demand accountability about their situative and evolution-based communicative expression and scientific evaluation within an accessible frame by using adequate and routinely applicable methods to broaden the therapeutic options and to further personalize therapy. In contrast to the theory of scale relativity [39], which is an extension of the theories of relativity (achieved by applying the principle of relativity not only to motion transformations, but also to scale transformations of the reference system), vagueness about the communicative expression in evolving tumor systems is directly mirrored in concurrent communicative features, the functional world, for instance, a cell and the systems world of a biologic cell community [40].
- **On the one hand, criticizable validity claims establish scientifically reproducible arrangements**, symbolized by the systems objects' references. On the other hand, such claims rely on the ever flexible reservoir of the systems participators' modular knowledge, which may implement the often surprising spin off of novel systems functions by the impact of externally- and internally-derived communicative processes [41, 42]. Validity claims must be raised in a time- and space-related context, which is founded in an inevitable situational rationalization of the tumor's living world, i.e., the tumor-specific risk-absorbing background. Validity claims are accepted or rejected with regard to non-reversible action sequences: Tumor cells may irreversibly destroy physiologically rationalized organ systems by colonizing the host's organs [27].
- **Idealizing suppositions:** The application of communication tools aimed at reaching understanding among systems objects demands idealizing suppositions including normative judgments on the part of communicatively linked actors. These scientifically underestimated suppositions function as social facts within a tumor's living world. The steadily generated social facts are constitutive—as are communication tools—for the form, in which situational social cellular life reproduces itself.

The attempt to reconstruct biologic communication processes and to show how to uncover and monitor these processes for therapeutic purposes cannot constitute a

comprehensive concept of a tumor's communicative tool of normative contents. What is at issue here is to discuss the daily diagnostic and therapeutic challenges—aimed at broadening the therapeutic instruments—on the basis of comprehensive and evaluable communicative presuppositions, which have been shown to be inevitable for the continuous and non-circumventable process of reaching communicative understanding as well as for strategic (therapeutic) communicative interventions. Reconstruction of prepositional reasons for differential rationalizations of systems within distinct evolutionary stages and the parallel uncovering of the respective situative procedural constitution of rationalization processes are of pivotal interest for broadening therapeutic options.

A formal pragmatic theory of meaning opens up possibilities to assess the scientific frame for possible choices of **tumor prevention and tumor therapy** by accentuating situational arising validity claims (Chap. 15). These claims constitute unconditionality by implementing rules, which are determined by situative propositions, as well as uncertainty about the communicative expression of a communication line during evolutionary tumor processes. Inevitably, prevention programs as well as programs trying to therapeutically reconstitute the 'status ante' before the disease, which is frequently symbolized by the achievement of complete remission, have to regard the propositional aspects of communicative expression promoted by communication lines and based on context dependent validity claims. Many routinely performed therapeutic interventions are afflicted with a **biological memory** (genetic and epigenetic changes), i.e., chemotherapy and radiotherapy [43, 44].

Pragmatic Implications for Systems-Oriented Therapy

Pragmatics describes the relation between communication lines as symbols (rich in content) and their respective effects on systems objects. Communication partners use the symbols (1) to constitute the inevitable phenomenological context (theory and practice), (2) to establish evolution by implementing modular knowledge, and (3) to maintain homeostasis by constituting robustness.

- **Homeostasis**, here defined as the sum of processes available to maintain normative notions, can only be explained on the basis of robustness, which is based on the multi-faceted 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: Still, a series of tumors are considered therapy-resistant [45].
- **Rationalizing the tumor's living world:** Of particular interest for the preservation of normative systems structures is the continuously proceeding process, by 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.

- **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-facetted rationalization processes to fail-safe constitute normative notions,
  - modular systems features by which a decoupling from the physical-chemical world may be established that is based on the redirection of validity claims by communication-derived rules.
- **Communicative strategic interaction,** characterized by implementation of non-normative boundary conditions ('top-down' approach) is opposed by 'bottom-up' strategies aiming at knocking down single pathways, oncogenes etc. (Chap. 2, 22). Using 'top-down' approaches, physicians are 'systems participators' via biomodulatory drugs. Strategic communicative action with 'top-down' approaches differs formally but not content-relatedly from 'bottom-up' approaches: To be efficacious, both approaches have to redirect the tumor's normativity. Basis for strategic biomodulatory interventions may be the multifold possibilities to therapeutically criticize communication-associated validity claims: (1) The propositions of the meaning of communication lines and (2) the perlocutionary acts (in linguistic terms), that means, the recourse on available communication lines, systems objects, or rationalization processes for maintaining normative notions with the aim to establish robustness and homeostasis.
- **The incommensurability between structure-oriented or theme-dependent configured systems and the action-oriented or evolution-adjusted systems 'world' ('living world') can be overcome** with the perspective of a pragmatic communication theory. Thereby, theory and practice may be bridged. Now, non-linear dynamics, i.e., the spin-off of novel systems functions and novel rationalization processes within a tumor's living world, may be explained on the basis of communicative interactions between systems participators. Situational phenomenological facts (disease traits) can be more precisely communicated by identification and continuous monitoring of changing identities of systems objects. Modified or even changing identities and denotations are associated with a frequently decisively altered functional impact of respective cell systems. Secretome analytics or molecular imaging—as described in a formal pragmatic communication theory—may be helpful to outline those changes [46, 47].
- **Time-related processes:** The 'system' can be shared by systems objects and presents itself phenomenologically in a situational context, i.e., 'the visible' [48]. The particular meaning of intra- and intercellular communication lines is strongly context dependent, and the situative phenotype may be broken down into differential rationalizations of the functional cellular and holistic communicative systems world. Consecutively, the monitoring of time-related processes

(time-consciousness) must be imminent in biological systems. The operative interplay of functional and systems world could be a main target for generating time-consciousness in biological systems.

Examining the Validity of a Communication Act

Reconstruction and monitoring of presuppositions and validity claims, which are inherent to biologic systems and their communication processes, are inevitable because the inescapable prerequisites and foundation of a system's communication practice come into sharper relief.

Systems objects within a **biologic system may modularly change** their references depending on the holistic communicative context. Modular knowledge of systems objects and rationalization processes, that means, the highly variably arranged rationalizations of normative notions (inflammation, angiogenesis, etc.), represent the 'metabolism' of evolving biologic systems.

Modular knowledge of systems objects is grounded in a continuously moving and communicative change of validity claims, which have to be customized for experimental evaluation. The social cellular or molecular world is neither treated any more as a given (in a reductionist sense) and routinely processed procedure nor viewed as a predetermined procedure: Contingency programming, education, modular rearrangement, and novel rationalization of normative notions are characteristics of communicatively evolving biologic processes mediated by the respective systems objects [27].

Communicative actions of systems objects cannot be left behind, if we want to close the obvious gap between theory and practice, between the static 'historic' systems object with its references and the communicatively integrated evolving systems subject [26]. The holistic communicative systems world, i.e., the living world, is actively participating in the implementation of rationality into biologic systems. The presuppositions shared by those systems objects, which are involved in a communicative biologic process, are now taken to reflect and to uncover validity claims with the aim to bridge therapeutic theory and practice.

Everyday therapeutic practices, such as strategic communicative interventions for reaching a purposive understanding of the systems objects of a lesion and its host, and the therapeutic redirecting of reasons for pursuing the lesion's course of pathologic actions now acquire idealized rationality.

Communication has always to be viewed as rational. Communication could not occur if we do not assume that the communication acts mediated by the systems objects do not carry the dimension of validity, for which these participating systems objects are accountable.

Uncovering Communication-Related Rules Requires Novel Analytical Methods

The communication-based reconstructive analysis of tumor systems biology directly disembogues into novel possibilities of interpreting the phenomenological and, therefore, expressive site of clinical proteomics [47]. What does it mean that a pathway, a communication line, is being or becoming stimulated?

Validity claims have to be depicted step-by-step on both a clinical and an experimental level. The facticity of such validity claims is shown by the capacity of modular therapy approaches to induce continuous response in metastatic tumor disease by redeeming and redirecting modular knowledge. Novel patterns of biomarkers indicate functional changes in tumor-associated cell communities in response to modular therapy approaches (e.g., clinical proteomics), and novel modular arrangements on the cellular level are symbolized by communicatively-derived 'fragments' [31, 32, 49]. These novel patterns and modular arrangements give further hints of how to control systems-associated processes with therapy modules to achieve objective response [15] and to adapt biomodulatory therapies to situative developments in metastatic tumors [5]. Furthermore, they allow an evolution-based systems interpretation [6] of how they could contribute to novel and more realistic in silico models.

Examples of Criticizable Claims of Validity

The therapeutic accessibility of validity claims of systems objects is impressively shown by biomodulatory therapy approaches: Within tumor-associated communication tools, systems objects may be integrated in a multifunctional way:

- **Autonomous and non-autonomous portions of transcriptional activation** in tumor 'stem cells' are accountable for differential tumor phenotypes (glioblastoma) and visualize the intersubjectivity of communication [45]. The nature of cancer stem cells may be considered as a state rather than an entity [50].
- 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 towards previous cellular functions or by the assignment of new functions [27].
- **Modular therapies** may supplement prepositional aspects of communication, i.e., the presence of a tumor's living world by normative aspects, namely by therapy-derived 'yes' or 'no' statements ('know that') [40]. The therapeutic efficacy of biomodulatory therapies support the presence of a therapeutically accessible holistic communicative tumor system that may be specifically targeted [14].
- **It is necessary to decode paradox situations** of cellular rationalization and communication expression, i.e., to uncover inconsistencies, bottlenecks, and deformations within tumor cell compartments by means of a theory that includes

the evolutionary development of a tumor as well as its biologic history to increase therapeutic options through systems-directed approaches. Achilles' heels may be functionally described as decoupling systems and a functional 'world' of tumor cell systems [27].

Systems Objects in Dynamically Rearranging Biological Systems

Systems objects are communicatively linked benchmarks, which may be understood by studying physical, chemical, structural, and functional characteristics, irrespective of whether molecules, pathways, or cell communities are taken into consideration.

Beyond these systematically ascertained facts, we adjudge the systems objects' modular knowledge. The modular knowledge of systems objects is primarily a biologically unknown quality, which cannot be necessarily predicted from physical-chemical characteristics in non-linearly evolving systems such as tumors [3, 15, 31, 32]. Modular knowledge describes the capacity of systems objects to get involved in context-dependent and highly situative functional rearrangements, which may significantly alter the validity and denotation of particular systems objects.

Evolution-Driven Situational Status

An evolution-driven situational status is featured by a highly specific modular arrangement of numerous molecular species, pathways, multi-faceted functions of available structures, and rationalization processes. A non-linearly developing situational status, symbolized by novel modular combinatorial arrangements, finally necessitates the reinterpretation of the meaning of communication lines in an evolution-based communicative context [26, 51].

General interpretations of the rules that guide modular biological processes do not obey the same categories of refutation as general theories about physical and chemical interactions, thus per se remaining open for discussion. The logic of an explanations of rules redeeming the validity and denotation of systems objects within a communicative cell community is the result of a connection between a hermeneutic understanding and causal explanations [15]. The capability to interpret situative observations by communication-associated rules, for instance by utilizing biomodulatory therapies, represents a prerequisite for understanding a particular and sometimes unique systems stage, constituted by primarily non-predictable arrangements of systems components (on the background of multiple tumor-associated acquired aberrations) and specified functions.

Validity Claims and 'Corrupt' Activities

Communication-associated rules relieve us from the need to interpret morphologic-structural and physical-chemical interactions to delineate modular communication-linked features of systems objects. Now we can directly describe empirically-derived rules involved in implementing modular knowledge of systems objects. For this purpose, we may neglect physical-chemical interactions among molecules or cells. Of interest is the validity claim of a systems object, which is grounded in the formal pragmatic communication theory and depicted in novel analytical approaches including mathematical specifications of modules or functional 'fragments' [31, 32].

Unique tumor-associated rationalization processes can also be considered as strategies that allow systems objects and the respective modular arrangements to establish their 'corrupt' activities as justified, based on validity claims [52]. Tumor-associated rationalization processes are frequently preserved in multiple metastatic tumor sites despite the commonly observed heterogeneity of chromosomal and molecular-genetic aberrations in tumor cells [53; Chap. 2].

The Origin of a Communicative Impulse is Therapeutically Relevant

'Knowledge of the molecular profile of the tumor is necessary to guide selection of therapy for the patient' [2]. This claim by Schilsky is unequivocally correct, but substantially constrains the use of the myriad of molecular tumor-associated data on the concept, such as one drug for one major high affinity and high specificity target and multiple drugs for several targets [3, 54–56]. However, these approaches turned out to be highly selective with regard to their clinical efficacy and thus failed to offer a broad rational solution for the majority of metastatic tumor diseases (Chap. 2, 7, 15).

The question is generally left unanswered whether a single target, pathway, or tumor-associated cell type really expresses the same validity claim in a primarily unknown situative status of a tumor just as in any discretionary experimental setting. Molecular genomic patterns could also correlate with distinct validity claims of systems objects or rationalization processes in a respective tumor, thereby indirectly contributing to the design of modular therapy strategies.

Knowledge of the validity claim of therapeutically relevant systems objects and concrete rationalizations of normative notions may be now supplemented by knowledge about the origin of a therapeutically relevant impulse. Modulation of the prepositions of an impulse relevant to fulfill important tumor-associated normative notions may decisively attenuate tumor growth [15] (Chap. 23). Thus, the major origin of tumor-associated inflammation, angiogenesis, etc. gain center stage when defining novel starting points for therapeutic interventions [23].

Overcoming Robustness

Diagnostic and therapeutic methods for overcoming robustness may now focus on the basic mechanisms contributing to biological robustness. In future, clinical proteomics data for reconstructing communication expression of systems objects may highlight the confliction of systems world and functional world and the recourse of systems on multi-faceted rationalization processes to fail-safe constitute normative notions and on the modular constitution of systems. A robustness-oriented design of therapy schedules, i.e., the appropriate combinatory use of biomodulatory acting drugs, affords novel patterns of functional biomarkers to efficaciously guide combinatorial complexity on the basis of validity claims of respective systems objects [47]. Monitoring robustness-related systems processes could enable us to systematically specify methods for the combinatory use of biomodulatory acting drugs [57, 58, Chap. 23].

Discussion

The discussion about validity claims of systems objects positions familiar structures, cell types, pathways, molecular aggregates, etc. as communication-derived subjects. Physical-chemical interactions do not lose their explanatory strength, but communicative systems behaviors may also be depicted by scientific evaluation of additional and so far less regarded rules: In the first place, validity claims put communicatively linked systems objects in an evolutionary context. Otherwise, ('historic') preclinically raised references in terms of systems objects or known communication lines may now be linked to a distinct and potentially novel communicative expression, i.e., their situative meaning. In non-linearly developing systems, such as tumors, the situative meaning of molecular-biologic and morphologic detectable systems objects may be significantly altered [9, 10].

Validity claims and their therapeutic accessibility have achieved the status of facticity by demonstrating the clinical efficacy of modular therapy approaches and the modulation of communication expression that means redirection of systems objects validity and denotation. Validity claims of systems objects, based on communicatively-derived presuppositions within a particular systems context, position preclinically-derived references of objects as individual tumor systems subjects, which may acquire novel denotations in non-linearly evolving tumor systems.

The presented reconstruction of tumor-associated communicative processes for reaching understanding or generating meaning follows the theories of Habermas, whose communication technical explications are much easier to integrate into biological processes because of their pragmatic attitude and apparent experimental as well as therapeutic replicability [58–61], than, for instance, the explanations by Piaget and Charles Sanders Peirce (object sign, representamen, interpretant).

As yet, an exclusive reconstructive analysis of communication-derived validity claims is unusual in biology. However, validity analyses of systems objects in a situative, evolutionary-based context reveal the necessity to open up multifold

novel therapeutic options, particularly for further personalizing tumor therapy. As an instrument for analyzing, we applied a formal pragmatic communication theory. Aim of the analysis was to exploit the potential starting points for therapeutic interventions with regard to modular therapy approaches and to strengthen the application and interpretation of parameters derived from clinical proteomics, for example, secretome analyses for uncovering novel functional biomarkers indicating changes in communicative expression of systems objects.

The new diagnostic field 'clinical proteomics' has the capacity to develop methods, which assess seemingly familiar communication lines from the site of their communicative expression [47]. The meaning of communication lines is closely linked with phenotypically accessible functions or functional changes upon modular therapy approaches [15]. Such a methodological approach goes far beyond the appreciation of the syntactical modeling grammar as a prerequisite for describing a formal logical syntax [62] or a mathematical work-up of data within a targeted therapy database [63]. The goal of assessing communication-derived rules redeeming and redirecting the respective validity claims of systems objects is to generate hypotheses, which may be pragmatically integrated into novel tumor models that can be more efficaciously used for personalized diagnostics, combinatorial drug design, and novel in silico programs.

Knowledge about modular arrangements, diverse rationalizations of systems functions, the origin of a communicative impulse within a tumor system, the tumor-specific recourse on rationalization processes during systems perturbations (robustness), and probably the therapeutic altering of time-consciousness generated by biological systems (presumably by cutting off instigating signals or redirecting biological memory) allow completely novel insights into communicative determinants of tumor systems biology and facilitate therapy design, which is now also orientated at the communicative context.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM (2010 Dec) Estimates of worldwide burden of cancer in GLOBOCAN 2008. Int J Cancer 127(12):2893–2917
2. Schilsky RL (2010 May) Personalized medicine in oncology: the future is now. Nat Rev Drug Discov 9(5):363–366
3. 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
4. Nguyen DX (2011 Jan) Tracing the origins of metastasis. J Pathol 223(2):195–204
5. Reichle A, Vogt T, Hildebrandt G (2010) A methodological approach to personalized therapies in metastatic cancer. In: From molecular to modular tumor therapy. The tumor microenvironment, vol 3, part 8. Springer, pp 507–533. doi:10.1007/978–90-481–9531-2_25
6. 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 9. Springer, pp 545–556. doi:10.1007/978–90-481–9531-2_27
7. 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

8. Clermont G, Auffray C, Moreau Y, Rocke DM, Dalevi D, Dubhashi D et al (2009) Bridging the gap between systems biology and medicine. Genome Med 1(9):88
9. Ravandi F, Cortes JE, Jones D, Faderl S, Garcia-Manero G, Konopleva MY et al (2010 April 10) Phase I/II study of combination therapy with sorafenib, idarubicin, and cytarabine in younger patients with acute myeloid leukemia. J Clin Oncol 28(11):1856–1862
10. Metzelder S, Wang Y, Wollmer E, Wanzel M, Teichler S, Chaturvedi A et al (2009 Jun 25) Compassionate use of sorafenib in FLT3-ITD-positive acute myeloid leukemia: sustained regression before and after allogeneic stem cell transplantation. Blood 113(26):6567–6571
11. Mahon FX, Rea D, Guilhot J, Guilhot F, Huguet F, Nicolini F et al (2010 Nov) 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(11):1029–1035
12. Falchi L, Rege-Cambrin G, Fava C, Donti E, Luzi D, Giugliano E et al (2010 June) 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(2):139–142
13. Gerber DE, Minna JD (2010) ALK inhibition for non-small cell lung cancer: from discovery to therapy in record time. Cancer Cell 18(6):548–551
14. Reichle A, Hildebrandt GC (2009) Principles of modular tumor therapy. Cancer Microenviron 2(Suppl 1):227–237
15. Reichle A, Hildebrandt GC (2008 Dec) Systems biology: a therapeutic target for tumor therapy. Cancer Microenviron 1(1):159–170
16. Urban Emmenegger ACuGB (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
17. De Bosscher K, Haegeman G, Elewaut D (2010 Aug) Targeting inflammation using selective glucocorticoid receptor modulators. Curr Opin Pharmacol 10(4):497–504
18. Ilse ME, Beck GHDB (2010) Molecular cross-talk between nuclear receptors and nuclear factor-êB. 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
19. Kaileh M, Vanden Berghe W, Heyerick A, Horion J, Piette J, Libert C et al (2007 Feb 16) Withaferin a strongly elicits IkappaB kinase beta hyperphosphorylation concomitant with potent inhibition of its kinase activity. J Biol Chem 282(7):4253–4264
20. Ndlovu N, Van Lint C, Van Wesemael K, Callebert P, Chalbos D, Haegeman G et al (2009 Oct) Hyperactivated NF-{kappa}B and AP-1 transcription factors promote highly accessible chromatin and constitutive transcription across the interleukin-6 gene promoter in metastatic breast cancer cells. Mol Cell Biol 29(20):5488–5504
21. Suttana W, Mankhetkorn S, Poompimon W, Palagani A, Zhokhov S, Gerlo S et al (2010) Differential chemosensitization of P-glycoprotein overexpressing K562/Adr cells by withaferin A and Siamois polyphenols. Mol Cancer 9:99
22. Vodovotz Y, Csete M, Bartels J, Chang S, An G (2008 April) Translational systems biology of inflammation. PLoS Comput Biol 4(4):e1000014
23. Wu FT, Stefanini MO, Mac GF, Kontos CD, Annex BH, Popel AS (2010 March) A systems biology perspective on sVEGFR1: its biological function, pathogenic role and therapeutic use. J Cell Mol Med 14(3):528–552
24. Yeung WWS, Young MKCH, Wong YH (2010) Functional impacts of signal integration: regulation of inflammation-related transcription factors by heterotrimeric G proteins. In: From molecular to modular tumor therapy: the tumor microenvironment, vol 3, part 3. Springer, pp 161–189. doi:10.1007/978–90-481–9531-2_9. 10 A.D.
25. Soper R, Hagemann T (2010) Shaping tumor associated macrophages: the role of NF-kappaB. In: From molecular to modular tumor therapy: the tumor microenvironment, vol 3, part 2. Springer, 97–110. doi:10.1007/978–90-481–9531-2_6

26. 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
27. 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
28. Mantovani A (2009 Jan 1) Cancer: Inflaming metastasis. Nature 457(7225):36–37
29. Habermas J (2000 Jan 31) On the pragmatics of communication. The MIT Press. ISBN-13:978-0262581875
30. Yang G, Xiao X, Rosen D, Cheng X, Wu X, Chang B et al (2011) The biphasic role of NF-{kappa}B in tumor progression and chemoresistance of ovarian cancer. Clin Cancer Res 17(8):2181–94. doi:10.1158/1078–0432.CCR-10-3265
31. Feret J, Danos V, Krivine J, Harmer R, Fontana W (2009) Internal coarse-graining of molecular systems. Proc Natl Acad Sci USA 106(16):6453–6458
32. Harmer R, Danos V, Feret J, Krivine J, Fontana W (2010) Intrinsic information carriers in combinatorial dynamical systems. Chaos 20(3):037108
33. Khalil IG, Hill C (2005) Systems biology for cancer. Curr Opin Oncol 17(1):44–48
34. Wagner GP, Pavlicev M, Cheverud JM (2007) The road to modularity. Nat Rev Genet 8(12): 921–931
35. Hartwell LH, Hopfield JJ, Leibler S, Murray AW (1999) From molecular to modular cell biology. Nature 402(6761 Suppl):C47–C52
36. Reichle A, Hildebrandt GC (2010) The comparative uncovering of tumor systems biology by modularly targeting tumor-associated inflammation. In: From molecular to modular tumor therapy: the tumor microenvironment, vol 3, part 4. Springer, pp 287–303. doi:10.1007/978–90-481-9531-2_13
37. 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
38. Kovacs IA, Szalay MS, Csermely P (2005) Water and molecular chaperones act as weak links of protein folding networks: energy landscape and punctuated equilibrium changes point towards a game theory of proteins. FEBS Lett 579(11):2254–2260
39. Auffray C, Nottale L (2008) Scale relativity theory and integrative systems biology: 1. Founding principles and scale laws. Prog Biophys Mol Biol 97(1):79–114
40. Reichle A (2010) Uncovering tumor systems biology by biomodulatory therapy strategies. In: From molecular to modular tumor therapy: the tumor microenvironment, vol 3, part 7. Springer, pp 469–481. doi:10.1007/978–90-481–9531-2_23
41. Lin C, Yang L, Tanasa B, Hutt K, Ju BG, Ohgi K et al (2009) Nuclear receptor-induced chromosomal proximity and DNA breaks underlie specific translocations in cancer. Cell 139(6):1069–1083
42. Raaijmakers MH, Mukherjee S, Guo S, Zhang S, Kobayashi T, Schoonmaker JA et al (2010) Bone progenitor dysfunction induces myelodysplasia and secondary leukaemia. Nature 464(7290):852–857
43. Franklin J, Pluetschow A, Paus M, Specht L, Anselmo AP, Aviles A et al (2006) Second malignancy risk associated with treatment of Hodgkin's lymphoma: meta-analysis of the randomised trials. Ann Oncol 17(12):1749–1760
44. Scholz M, Engert A, Franklin J, Josting A, Diehl V, Hasenclever D et al (2011) Impact of first- and second-line treatment for Hodgkin's lymphoma on the incidence of AML/MDS and NHL–experience of the German Hodgkin's lymphoma study group analyzed by a parametric model of carcinogenesis. Ann Oncol 22(3):681–688
45. 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
46. Griss J, Haudek-Prinz V, Gerner C (2011) GPDE: A biological proteomic database for biomarker discovery and evaluation. Proteomics 11(5):1000–1004

47. Verena Paulitschke RKaCG (2010) Secretome proteomics, a novel tool for biomarkers discovery and for guiding biomodulatory therapy approaches. In: From molecular to modular tumor therapy: the tumor microenvironment, vol 3, part 6. Springer, pp 405–431. doi:10.1007/978-90-481-9531-2_21
48. STRAUS EW (1951) The autonomy of questioning: considerations of the psychological foundations of the human world. J Nerv Ment Dis 113(1):67–74
49. Walter B, Schrettenbrunner I, Vogelhuber M, Grassinger J, Bros K, Wilke J, Suedhof T, Berand A, Wieland W-F, Rogenhofer S et al (2010) C-reactive protein as a secretome-derived biomarker for predicting response to biomodulatory therapy in metastatic renal clear cell carcinoma. From molecular to modular tumor therapy: the tumor microenvironment, vol 3, part 5. Springer, pp 353–366. doi:10.1007/978-90-481-9531-2_17
50. Zipori D (2004) The nature of stem cells: state rather than entity. Nat Rev Genet 5(11):873–878
51. Reichle A, Hildebrandt GC (2010) Searching for the 'metabolism' of evolution. 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
52. Stelios C. Zyglidopoulos PJFaSR (2011) Rationalization, overcompensation and the escalation of corruption in organizations. J. Bus Ethics 84(Supp 1):65–73. doi:10.1007/s10551-008-9685-4
53. Remark R, Alifano M, Cremer I, Sautès-Fridman C, Fridman WH, Damotte D (2012) Composition, organization and clinical impact of the adaptive and innate immune microenvironments in lung metastases from colorectal and renal cell carcinoma. CSH Asia/ICMS Joint Conference on Tumor Microenvironment. Conference program symposium S4–S6 (abstract). http://www.csh-asia.org/Programs/2012Programs/a-tumor%20Program_colorFORWEB.pdf
54. Chang JT, Carvalho C, Mori S, Bild AH, Gatza ML, Wang Q et al (2009) A genomic strategy to elucidate modules of oncogenic pathway signaling networks. Mol Cell 34(1):104–114
55. Gatza ML, Lucas JE, Barry WT, Kim JW, Wang Q, Crawford MD et al (2010) A pathway-based classification of human breast cancer. Proc Natl Acad Sci USA 107(15):6994–6999
56. Kitano H (2007) A robustness-based approach to systems-oriented drug design. Nat Rev Drug Discov 6(3):202–210
57. Kitano H (2003) Cancer robustness: tumour tactics. Nature 426(6963):125
58. Laubichler MD (1999) A semiotic perspective on biological objects and functions. Semiotica 127:415–432
59. Habermas J (1985) The theory of communicative action, vol. 1. Beacon. ISBN-13:978-0807015070
60. Flavell (1963) The developmental psychology of Jean Piaget. Van Nostrand, New York
61. Pierce CS (1977) In: Hardwick C. Bloomington IN (ed) Semiotics and significs. Indiana, University
62. An G (2006) Concepts for developing a collaborative in silico model of the acute inflammatory response using agent-based modeling. J Crit Care 21(1):105–110
63. Mocellin S, Shrager J, Scolyer R, Pasquali S, Verdi D, Marincola FM et al (2010) Targeted therapy database (TTD): a model to match patient's molecular profile with current knowledge on cancer biology. PLoS One 5(8):e11965