

# Principles of Modular Tumor Therapy

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**Abstract** Nature is interwoven with communication and is represented and reproduced through communication acts. The central question is how may multimodal modularly acting and less toxic therapy approaches, defined as modular therapies, induce an objective response or even a continuous complete remission, although single stimulatory or inhibitingly acting drugs neither exert mono-activity in the respective metastatic tumor type nor are they directed to potentially ‘tumor-specific’ targets. Modularity in the present context is a formal pragmatic communicative systems concept, describing the degree to which systems objects (cells, pathways etc.) may be communicatively separated in a virtual continuum, and recombined and rededicated to alter validity and denotation of communication processes in the tumor. Intentional knowledge, discharging in reductionist therapies, disregards the risk-absorbing background knowledge of the tumor’s living world including the holistic communication processes, which we rely on in every therapy. At first, this knowledge constitutes the validity of informative intercellular processes, which is the prerequisite for therapeutic success. All communication-relevant steps, such as intentions, understandings, and the appreciation of messages, may be modulated simultaneously, even with a high grade of specificity. Thus, modular therapy approaches including risk-absorbing and validity-modifying background knowledge may overcome reductionist idealizations. Modular therapies show modular events assembled by the tumor’s living world as an additional evolution-constituting dimen-

sion. This way, modular knowledge may be acquired from the environment, either incidentally or constitutionally. The new communicatively defined modular coherency of environment, i.e. the tumor-associated microenvironment, and tumor cells open novel ways for the scientific community in ‘translational medicine’.

**Keywords** Evolution · Inflammation · Metastatic tumor · Personalized therapy · Systems assessment tools · Systems biology

## Introduction

Nature is interwoven with communication and is represented and reproduced through communication acts. As communication is a process covering all cell communities, also those in tumor tissues, it seems to be difficult to imagine that particularly cancer diseases originate from an equipollent cell only. Therefore, considerations about communication processes within the tumor compartment have to start with the central question whether an equipollent, communicatively structured tumor microenvironment is necessary rather than individual cells causing specific cancer diseases.

Single molecular changes in cancer cells, as specific as they may be, only lead to the development of specific malignancies, when they actively communicate on a sub-cellular level to finally alter cellular behavior and when adjacent cell types acknowledge the communicated information in a sense the originator intended. This communicative act must allow and must be responsible for the reorganization of well-established normal tissue. Further, in view of the differential steps of communication, the cell community in tumor tissue, which is represented as a

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holistic communicative system, is also a critical part determining the functionality (quiescent, tumor-promoting phase) of cancer (stem) cells and the development of cancer disease.

Consecutively, tumor development may be described as pathological communication processes on the tissue, the cellular, and the molecular level. Complex biochemical networks are mediators of cellular communication and, considering the multiplicity of tumor-associated communication processes we should include the sub-cellular complexity of biochemical networks as a target into novel concepts of therapeutic approaches.

Transcription factors with their concerted activity are central regulators of sub-cellular communication processes. Their complex integration into the sub-cellular context is best characterized by their often chimera-like function, equivalent with their communicative integration within networks, which constitute multifold systems functions within the tumor tissue. Dependent on distinct circumstances (the often unconsidered ‘background’), they may exert cell type-dependent opposing biological effects. Consequently, a major challenge is to elaborate how single communication processes acquire validity and distinct denotations on the background of numerous input signals discharging into specific biological responses that control tumor evolution.

Up to now, frequently used tumor therapies aim at blocking distinct communication processes involved in tumor promotion, for instance, by changing the denotation of a distinct communication-associated pathway in tumor or stroma cells or by directly targeting and eliminating the bulk of tumor cells (monoclonal antibodies). Successful examples of ‘magic bullets’ (Paul Ehrlich) in standard clinical care in hematology are, for instance, tyrosine kinase inhibitors in chronic myelocytic leukemia and monoclonal CD20 antibodies in B-cell lymphomas [1, 2]. The underlying idealizations with regard to the manner of how to use therapeutically relevant changes in denotations of ‘tumor-specific’ pathways refer to a well-rehearsed coherency of interactions that should fulfill practical and, at best, tumor-specific functions. Therefore, therapeutic approaches in tumor therapy are predominantly designed in a reductionist way [1].

Previous modes for therapeutically modifying communication processes in metastatic tumors included, for instance, the use of small molecules, monoclonal antibodies, or cellular therapies. The modes were based on the intentional comprehension of these communication processes [1], presuming what distinct communicating cells generally (i.e. under generalized conditions) insinuate with a signal used in a given situation. This way of generalizing validity of an addressed signal distracts from the often situatively complex biochemical conditions that make a

signal valid in the first place. Context-related changed validity of transcription factors and consecutively altered denotations are exceptional examples.

The dimension validity of a communication process is introduced by formal communication theories that are trying to assume circumstances under which a communication process is or becomes valid. Although acknowledgement of validity is a prerequisite of communication processes, the functional and structural premises for redeeming validity are commonly discussed to a far lesser extent, if not neglected altogether [3–5].

The communication theory developed in this paper is anchored in observations derived from controlled clinical trials on the use of a combination of biomodulatory acting drugs (= systems-directed therapies) in a broad variety of metastatic tumors [6]. Reductionist considerations may not explain how multimodal, less toxic systems-directed therapies are able to induce an objective response, even a continuous complete remission, although single stimulatory or inhibitingly acting drugs (i.e. modulators of transcription factors) do neither exert mono-activity in the respective metastatic tumor type and nor are they directed to potentially ‘tumor-specific’ targets [6]. As an explanation for the activity of these biomodulatory therapy approaches, we introduced a new communication-technically paraphrased term as target for the cumulative functional activity of systems-directed therapies known as tumor-specific ‘topologies of aggregated action effects’ [6]: Systems-directed therapies may primarily neglect tumor-related activities that seem to be operationally induced by the division of function, such as inflammation, neoangiogenesis, Warburg effect, immune response, extra-cellular matrix remodeling, cell proliferation rate, apoptosis, and coagulation effects. From a systems perspective, these differential activities present themselves as an enhancement of complexity [6]. Their presenting character turns out to be primarily communicative, as shown in the methodological discussion.

Communication-technical considerations will be helpful to uncover mechanisms of action of modularly designed therapy approaches and to conceptualize how this novel way of treatment modulates sub-cellular and cellular communication. At first, these considerations involve a theory relating to communicative aspects of socially linked cell communities, such as the tumor compartment. The theory is also supported by observations derived from a unique pattern of modular therapies administered in a broad variety of metastatic tumors [6].

This theory leads to the question how communication processes may be initiated (therapeutic aspect) in the context of the basic components of the communicative ‘metabolism’, which foster natural or therapeutically adjoined but implicitly evolutionary-linked tumor develop-

ment. Induction of novel validity in informative cellular or intercellular communication processes by modular events may be an important mechanism promoting tumor evolution or treatment.

### Methods: A Formal-Pragmatic Communication Theory

Clinical results used to support the formal-pragmatic communication theory refer to recently published data [6].

#### Definition of the Tumor's Living World as a Holistic Communicative Unit

Exemplarily for cellular transcription factors, their context-dependent and cell type-specific transcriptional activity illustrates the meaning of the term modularity. The activity is mirrored on a cellular level by the multi-functionality of, for instance, macrophages or fibroblasts.

Modularity in the present context 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 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 which are able to acquire novel references by rearranging validity and, consecutively, denotation. Tumors consist of modules, which become a scientific object by communicatively uncovering the tumor's living world (defined as the tumor's holistic communicative world) with biomodulatory and therefore modularly designed events (for instance biomodulatory therapies).

Modularity 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 (holism of the tumor's living world): The systems 'metabolism' modularly and non-randomly changes validities and denotations of biochemical and biological processes. Modularly induced evolutionary steps advance the classic definition of evolvability as the capacity of an organism or a biological system to generate new heritable phenotypes [7] by evolvability within the tumor's living world.

#### Situative Objectivation of the Tumor's Living World

We, and the smallest living units, i.e. socially interconnected cell communities, are 'born' to communicate. To describe intercellular communication features, we are constrained to terms borrowed from appraising interpersonal relations: Cell systems are getting instigated, educated, reeducated, and attracted, and addressed cells may even be subject to fallacies [8–12]. These few samples, describing different modes of agreement by an addressee or an addressing cell unit, show communication processes that are more than the appreciation of signals independent of the level of communication. Prerequisite for the following discussion is that we assign a single cell communication competence on the background of its genetic repertoire.

Communication processes with their occasionally complex facets of appreciation and generation of agreement might be considered constitutive in nature. However, the question arises whether differentially designed and therapeutically aligned communication procedures, such as modular therapy approaches, have the ability to objectify interrelations and communication structures between basically communicatively associated and evolutionary developing cell communities, such as tumors. If so, a second and now situative objectivation could be generated besides the intentionally acquired previous context-dependent knowledge.

Addressing the question which background communication processes may be initiated in tumors first, for instance, to alter the validity and denotation of transcriptional processes, requires a clarification of the single steps of communication from an intentional point of view (communication theory). In a second step, we have to explain the background which principally allows the commonly used reductionist therapy approaches to uncover the so far frequently unconsidered risk-absorbing background 'knowledge'. This knowledge reassures systems robustness as illustrated by recovery from reductionist therapeutic interventions for tumor control. Tumor's robustness may be specifically responsible for poor therapeutic outcome, and robustness may absorb severe therapy-induced toxicities in a patient's organism.

How may the social organization of a tumor be possible? If modular events, similar to modular therapy approaches, tie the holistic communicative activity of a tumor, a 'social' action theory could be derived, which may objectify the 'metabolism' of evolving evolutionary systems. An analysis of the prerequisites for communicative action seems to be necessary to exploit the dimension of the living world's background, which cross-links and stabilizes larger cell communities, such as tumors.

## Formal-Pragmatic Theory About Denotation of a Communication Process

A formal-pragmatic theory about the denotation of a communication process may establish an internal interrelation of denotation and validity.

**Intention** is inherent to all messages, also in those of intercellular communication. The understanding of a signal or a more complex message by the addressed cell is a prerequisite for the requested appreciation of a message.

**Appreciation** is a normative notion, dominant and rich in content, which reaches out to the understanding of, for instance, transcriptional cascades, which may be context-dependently assessed as a ‘grammatical’ phrase. The understanding of a cellular signal, which has been perceived as valid, is not equivalent with the appreciation of an addressed intention (agreement, disagreement, refusal, etc.). Signals, which are perceived as valid and valid signals should be differentiated.

If appreciation is established, for example, in an agreement, both sites of an intercellular communicative exchange have to accept the respective communication process as appropriate. Appreciation assesses the intercellular acknowledgement of the validity of a basically criticizable intercellular communication process.

Denotation issues cannot be completely separated from validity issues. The denotation-theoretical question ‘what does it mean to understand a communication process’ cannot be isolated from the question under which circumstances a communication process may be considered to be valid.

## Perception of Validity

A cell would not know what it means to understand the denotation of a communication process, if it did not know how to help itself to agree on something with other cells. The prerequisites for communicative comprehension via transmitters, ligands, cytokines, and hormones, etc. may already appreciate that the communicative activity, which may be established with their help, is directed to the comprehension of a transmitted message. That means, as long as a ‘tumor cell’ does not find a comprehensive cellular surrounding or may not traffic suitable cell types in its adjacent surroundings, it may not function as a tumor cell. Therefore, also disabling comprehension within communication pathways may be a therapeutic aim.

The communicative activity of many molecules and communicative structures is context-dependent with regard to the validity and denotation within a communication process; for instance, single NF-kappaB signaling pathway can perform multiple biological functions even in the same clonal populations. This phenomenon may be assessed for

many transcriptional processes [13–17]. The communication process itself may be hedged by highly variable cellular communication architectures (synapses, gap junctions, receptors, pathways, transcription factors, acetylation modifiers, etc.).

## Novel Idealizations: Therapeutically Relevant Redemption of Validity

A method for redeeming the therapeutic validity of communication processes by administration of modular therapies requires idealizations that are present in the living world of a tumor (holistic communicative activity of a tumor). These idealizations exclusively unfold their effectiveness within tumor-associated communication processes. Cells have access in form of explicit knowledge on the background of their (epigenetically modified) genetic repertoire. 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 [18].

At first, this background knowledge about the tumor’s living world represents scientifically none-thematized, situative, speculative, horizon-knowledge. We implicitly rely on this risk-absorbing knowledge in every therapeutic intervention. The background knowledge covers the many assumptions we silently make based on a speculative horizon.

The background knowledge about the living world is subjected to conditions of scientific comprehension: Intentional ways fail to describe risk-absorbing knowledge, in which context-dependent knowledge about commonly administered reductionist therapy approaches is rooted, and the network of the holistic communicative activities turns out to be the medium through which the tumor’s living world is mirrored and generated.

In an evolutionary developing tumor system, the idealizing potency lies in the therapeutic anticipation of physicians: Communicative actions (modular therapeutic interventions) are now an element of a cycle process, in which the physician is likewise a product of current knowledge and tradition. Therefore, tumor systems biology may not be generally interpreted in context-free explanations [6].

*Holistic character of communication* Each communication-initiated activity is linked via communication-technical relations with many other communication-initiated activities. The knowledge about a communication technique (modular therapy) is interwoven with the knowledge about

**Table 1** Therapy modules

	Module A (lead-in)	Module M	Module A/M	Module A/M plus dexa	Module A/M plus interferon-a
Melanoma*** (randomized)	+	+	+	–	–
Gastric cancer*** (ran.)	–	+	+	–	–
RCCC*** (sequential)	–	–	+	–	+
HRPC**	–	–	–	+	–
Sarcoma**	+	–	+	–	–
LCH**	–	–	+	–	–

A = pioglitazone 60 mg daily plus rofecoxib\*\* 25 mg daily or etoricoxib\* 60 mg daily

M = trofosfamide\* 50 mg thrice daily, or capecitabine\*\* 1 g/m<sup>2</sup> or 1 g absolute twice daily for 14 days every 3 weeks

Dexa = dexamethasone 0.5 or 1 mg daily

Interferon-alpha 3 or 4.5 MU thrice weekly

the behavior of the communicatively uncovered living world of a tumor.

### Implementation of the Formal-Pragmatic Communication Theory

Exploitation of Background Knowledge  
About The Tumor's Living World: Disrupting  
the Holistic Communicative Thicket

A formal-pragmatic communication theory is provided to explain the therapeutic efficacy of drug combinations characterized by exclusively combined biomodulatory activity and no or poor mono-activity.

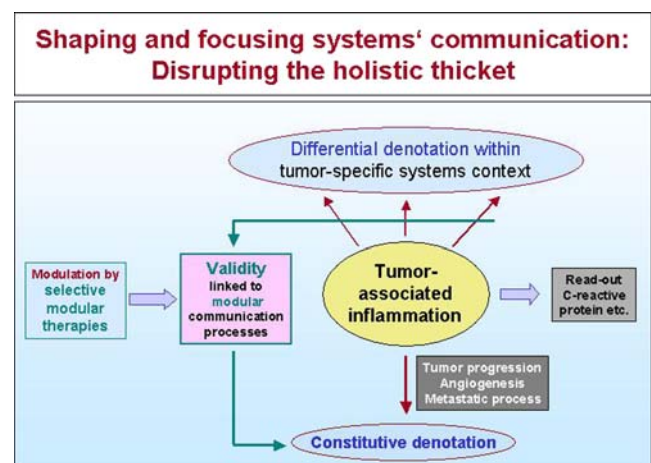
### Clinical Results Supporting a Formal-Pragmatic Communication Theory

If modularly designed therapies particularly target communicatively linked systems, i.e. their modularity as represented by a distinct systems response (e.g. attenuation of inflammation), modularity should be indicated by unique systems-associated biomarkers. Vice versa, identical modular systems should be accessible for different biomodulatory designed therapy approaches because of the tumor- or situation-dependent variation of cellular promoters of modular systems [17, 19].

As shown in Table 1, modular systems architecture of metastatic tumors could be uncovered by a small set of biomodulatory therapies. Differentially designed therapy modules were able to uniquely induce a response in serum C-reactive protein (CRP) levels of patients across a broad variety of metastatic tumors (Fig. 1): the observed CRP response preceded or was closely linked to clinical tumor

response (stable disease >3 months, partial remission, or complete remission). This demonstrates that tumor-promoting pro-inflammatory processes are differentially accessible from a communication-technical point of view and differentially constituted in their modularity. Nevertheless, CRP may serve as a unique modularly-linked systems marker to early show the efficacy of these therapies [6].

Most cells within the tumor compartment are constrained to respond to administered modular therapies: targeted molecules are ubiquitously available and partially constitutionally expressed, particularly certain receptors targeted with their respective stimulatory ligands, such as the glucocorticoid receptor, and peroxisome proliferator-activated receptor alpha/gamma. Consequently, many cell systems are included in processes, which may modify modularity and consecutively evolvability. Clinically, this



**Fig. 1** Shaping and focusing systems' communication: Disrupting the holistic thicket

kind of activity is supportively reflected by tumor responses, which occur within a strongly delayed time frame following biomodulatory therapies [6].

Stage-specific and tumor-specific dysregulation of PPARgamma and COX-2 expression in tumor cells are now well established in a broad variety of tumors [20]. Tumor-associated dysregulation of transcription factors (modular communication-technical background) in tumor and stroma cells may be addressed by biomodulatory therapies, such as low-dose metronomic chemotherapy in combination with or without transcriptional modulators (dexamethasone, interferon-alpha, cyclooxygenase-2 inhibitor (PPARdelta), and pioglitazone; Table 1) [6].

High PPARgamma expression was shown to be representative for the possibility to achieve modular response (improved survival) with different therapeutic approaches (metronomic low-dose chemotherapy plus or minus pioglitazone and rofecoxib) [20]. Notably, metronomic chemotherapy does not even directly target PPARgamma expression, and clinical response to therapy is not linked to inflammation control [21]: therefore, differential modular systems may be targeted to achieve clinical response.

Therapeutic systems-directed interactions mediated by modular therapies may basically interfere within the horizon of living worlds of organisms constituted elsewhere and its organs as well as with tumors. Therapeutic specificity may be achieved by the possibility of modifying the tumor's holistic communication system without significant organ-related side effects, as indicated by a large series of clinical trials [6].

#### Translation of Clinical Results in a Formal Communication Theory

Translated into a formal communication theory, administered biomodulatory therapies do not directly alter denotations of distinct pathways, such as reductionist designed 'targeted' therapy approaches, but redeem novel validity of modularly induced informative communication processes embedded into the tumor's living world. Modularity is shown to be a specific systems feature, which may be operationally uncovered and defined by distinct biomodulatory drug combinations.

At first, from a clinical point of view, the question how validity is redeemed with biomodulatory approaches on a molecular or cellular basis seems to be of minor importance, whereas particularly the 'know that', the normative communication-linked question is therapeutically critical because of the possibility of bringing about therapeutically relevant yes or no statements.

With regard to the 'know how', direct blocking of pro-inflammatory signaling pathways by the administered biomodulatory therapies may be excluded as the only

explanation for the clinically observable effects. Therefore, decisive changes in the prerequisites of validity of, for instance, pro-inflammatory processes have to be suggested. Changes of validity are implicitly linked with changing denotations of communicative processes, such as the attenuation of tumor growth.

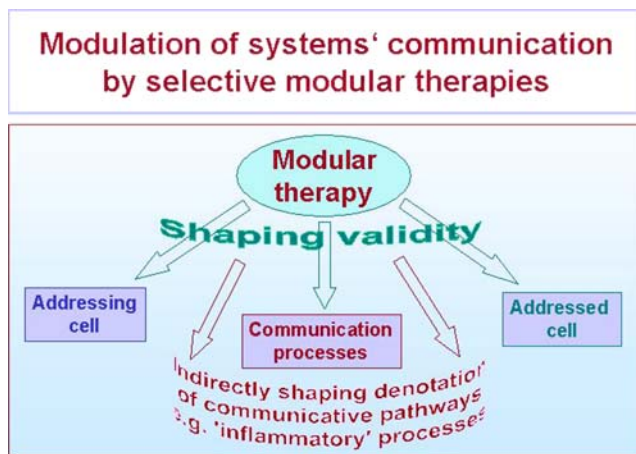
One molecular basis could refer to the cell type-specific combinatorially and dynamically shaped validity and denotation of protein complexes involved in cellular communication networks: NF-kappaB signal transduction pathways may regulate contradictory cellular responses in different cell types and, as recently shown, even within the same clonal population (i.e. cell proliferation versus differentiation and survival, immunity, and inflammation). Controlling factors of the function of NF-kappaB signal transduction pathways involve time, cellular conditions, and external circumstances [17]. However, specifically the latter are insufficiently understood, and this particular background knowledge could be uncovered by biomodulatory therapies on both a cellular and a tissue level.

At this point, the quantitative and qualitative assessment of biochemical processes in a systems context comes into play to prove and advance the formal-pragmatic communication theory on a biochemical level. This way, computational models on the whole tumor tissue's cell-type-specific 'omics' data could be rooted in direct systems biological observations, which may be derived from modular interventions (therapy approaches). Up to now, the direct assignment of communication-relevant validity and denotation modulating biochemical processes in distinct cell types is only fragmentarily assessable.

For therapeutical purposes, inflammation is often symbolized by the classical pro-inflammatory cytokines IL-6, IL-1, and TNFalpha, irrespectively of the cellular sources releasing these cytokines and the cell types calling out for response [22]. However, modular therapy approaches, which include the risk-absorbing, validity modifying background knowledge into the therapeutic calculus, may overcome these reductionist idealizations as all communication relevant steps (intention, understanding, appreciation of messages) and the differential tumor-associated promoters of communication may be simultaneously modulated (Fig. 2) [6].

#### Explication of a Formal-Pragmatic Communication Theory

The claims for redeeming novel therapeutic validity are not only directed towards therapeutic success but also tailored on the relation of communication to the objective features of the tumor compartment, the evolutionary developing modularity of a tumor, as tumor-associated pro-inflammatory processes, for example, are differentially integrated into the modular architecture (Fig. 1).



**Fig. 2** Validity of communication processes may not be considered as a quality, which is independent of the objective relation between communication and perception of the tumor microenvironment

Modularity may allow the retrospective establishment of spaces for evolutionary developments if modular events (therapy) are implemented. Simultaneously, the background of the tumor-associated living worlds loses its action-guiding function as consensus-warranting evolutionary-driven resource. The communicative interaction structures are now the objects of an actor (physician), who brings about distinct reactions in tumor processes, characterized by specification of tumor systems' denotations via redeeming novel validity (Fig. 1).

*Objectivation of the tumors' living world* Modular therapies may be the communicative medium for establishing novel validity of communication-driven processes within the tumor's living world by the rearrangement of protein complexes, altered release of mediators, etc. (Fig. 1). Modular therapies may supplement propositional aspects of communication, i.e. the presence of the tumor's living world by normative aspects, namely by therapy-derived yes or no statements ('know that'): Assigned to the function of transcription factors, the changing 'background' may critically determine their validity and denotation in a situation-related manner.

*Sustainability of modular therapy* Besides the possibility for redeeming novel validity (for instance inflammation control), modular therapy approaches are characterized by sustainability as indicated by frequently observed late objective tumor response [6].

*Communicative systems architecture* The matter of validity of intercellular communication processes may not be considered anymore as a matter detached from the objective relation between communication and knowledge about

cellular behavior. From a therapeutic view, the possibility for redeeming validity marks the change from the 'know how' to the 'know that': Knowledge about the tumor and communicative knowledge (modular systems) are integrated into one another. Therefore, therapeutic options about clinically relevant modular communication techniques are linked with the knowledge of how the communicatively accessible living world really behaves (communicative systems architecture).

*Function of modular communication* The therapeutic modulation of validity is aimed at achieving novel denotations of communication processes [17]. The dimensions' denotation and validity are internally tightly related within communication processes. The function of modular communication is to configure the coherence between validity and denotation. Thereby, novel denotations may be therapeutically tailored via modulation of validity processes (e.g. tailoring validity of pro-inflammatory processes for tumor control). Mediators of these communication processes are communication-related molecules, pathways, protein complexes, etc., whose denotation may be situatively exchangeable to some degree or is subject to decisive modifications in a non-random communicative tumor systems context embedded in the tumor's living world.

*Specificity of redeemed communicative validity* Specific conditions of compliance for redeeming validity on the site of the tumor's living world constitute relations between communication technique (specified modular therapy approaches) and distinct tumor-associated situation-engraved systems stages. Modular therapies in different metastatic tumor types show a high grade of specificity for redeeming novel validity via modular therapy elements [6].

Differentially redeemed validity of modular events (therapy approaches) represents the convergence point that facilitates (clinically) important yes or no statements. Not until then does the communicative situation allow a second objectivation of the tumor by uncovering the tumor's living world. Modularly changing validity and denotation of components of the tumor's living world represent the dimensions fostering evolutionary processes in tumor development, for example, the link between tumor-associated inflammation and tumor progression.

*Tumors constitute a solitary world with an internal context* This solitary world is represented by highly specific topologies of aggregated action effects. As indicated by moderate systemic toxicity profiles of the administered modular therapies, these action effects obviously need to be clearly separated from those appearing in a normal organ context.

Systems-related biomarkers, such as C-reactive protein in serum or PPARgamma expression in tumor cells, may

guide modular therapies. Corresponding systems changes may be closely linked to clinical response after modular therapy. Therefore, the redemption process of a novel therapy-guided validity may be followed early in the therapeutic process by indicators specifically associated with functional changes in single systems features. Interestingly, the validity of prognostic markers in malignant tumors can change with the tumor stage as demonstrated for COX-2 expression and PPARgamma expression in melanoma cells [20].

*Tumors are integrated systems* Randomized trials clearly indicate that tumors may be described by communicatively integrated and interwoven systems: In melanoma, both metronomic chemotherapy and pioglitazone plus rofecoxib independently develop clinical systems-directed activities and even seem to act synergistically [21]: Tumor-specific topologies of aggregated action effects may be specifically targeted with differential modular approaches to enhance therapeutic efficacy as tumors are composed by various modular elements, which are drawn into inter-systemic exchange processes (possible synergism).

*The modularity of a tumor is an independent tumor characteristic* As described, the modular systems concept does not follow the classic systems perception of functional pathophysiology. It is exclusively communication-derived and guided by redeeming novel validity through modular therapy approaches. Besides histology or molecular pathology, the modularity of a tumor is an independent tumor characteristic [6]: Tumors are additionally represented in a modular communicative architecture. The modular architecture of tumor-associated cell systems is directly embedded in the holistic totality of the tumor's living world.

*Modular therapy approaches may be designed tumor-specifically and stage-specifically (Table 2)* The advantage of a modular view of therapeutic interventions is the situative reference in topologies of aggregated action effects. The therapeutic value of the topologies of aggregated action effects lies in the presentation character of current communicative circumstances.

**Table 2** Modular therapies

- 
- Combined transcriptional modulation
  - Metronomic chemotherapy
  - Epigenetically modulating drugs
  - Combine therapies including biomodulatory acting drugs without or with poor monoactivity (indication discovery)
  - Combination with reductionist approaches?
  - Sequential modular–reductionist therapies?
- 

*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, for example, indicated by differential impact of pro-inflammatory processes within the tumor system [6]. Modular events (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 structures: Consecutively, communicatively derived systems may be described by rationalization processes, deformations, and intercellular exchange [6].

*'Metabolism' of evolution* How may new systems properties emerge? The possibility for redeeming novel validity shows the modulation of validity as an important evolutionary promoter (the 'metabolism' of evolution). The formal-pragmatic communication theory is able to establish modular coherency between environmental tumor cell-associated and microenvironment-associated communication processes as well as a modularity-based evolvability of systems.

*Reproductive structures* As the most meaningful reproductive structure we commonly suggest the genetic repertoire. Modular therapies now show that modular events, assembled by the tumor's living world, seem to present an additional evolution-constituting dimension, which primarily lies within the limits of the genetic repertoire. Additionally, also the heritable inventory might be evolvable. This way, modular knowledge may be either incidentally or constitutionally acquired from the environment.

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' may be successfully constituted by a formal pragmatic communication theory.

## Discussion

The living world of malignant tumors creates the term opposite to those idealizations, which originally constitute scientific knowledge.

'Commonly', W. Kolch remarked, 'we try to find out the function of a system by disassembling it and measuring the activity of isolated components. This approach is very successful in characterizing the individual parts but very limited in reconstructing the function of a system as a



whole' [23], suggesting that the systems concept as antithesis to reductionist concepts remains fully consistent with reductionist scientific approaches.

A holistic communication-based model termed the tumor's living world now opposes reductionist systems approaches. This world is uncovered by redeeming validity of communicative tumor processes through the implementation of modular knowledge on 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. In the first half of the 20th century, the biologist Spemann already characterized evolutionary systems in a communicative context: 'Reciprocal interactions may play a large role, in general, in the development of harmonious equipotential systems [24].

Modular therapies represent an alternative therapeutic solution compared to reductionist designed approaches. 'Systemic' therapies in a reductionist sense are designed by combinations of modifiers of pathways, which are more or less tumor-specific, and their rationale is usually based on analytics of pathway signatures [25].

In modular therapies, the communicative complexity of tumors, i.e. the multifold divisions in functions and structures, mirrors the modularly structured totality of tumor-specific communication processes. The present model, a formal-pragmatic communication theory, may now explain the therapeutic efficacy of exclusively biomodulatory acting drug combinations (stimulatory or inhibitory acting drugs, which do not exert mono-activity in the respective metastatic tumor type and are not directed to potentially 'tumor-specific' targets) in a modularly and evolutionary context. These findings recall the famous remark of Dobzhansky, 'nothing in biology makes sense except in the light of evolution' [26].

The important new step in our novel concept of understanding tumor biology and tumor evolution is the introduction of the tumor's living world as a holistic and therefore self-contained communication process in its idealization, in which external, communication-guiding interferences (modular knowledge) may be implemented to differentially focus on the coherency of the communication-technically, all-important dimensions validity and denotation. Now, mostly generalized tagged references derived from context-dependent knowledge about single communication-mediating cells, molecules, or pathways may be virtually neglected for communication-technical purposes [6]. These systems objects may be perceived as symbols in a continuum, rich in content, whose validity and denotation may be exchangeable but not at random.

This way, the tumor's living world is turning into a scientific object that becomes accessible for experimentally or therapeutically designed modular approaches for uncov-

ering the tumor's modularity. This modularity is defined by a distinct communicative architecture but also by the way how modularity has been communicatively uncovered.

Inclusion of prepositions for validity, which are present in the living world, and the implicit interplay of validity and denotation, which may be focused on modular events, afford transparency, how evolutionary processes may be first induced in the range of their molecular-genetically defined backbone. Imposed modular acting events, such as modularly designed therapies, may induce significant modular response in socially linked cell systems (prerequisite) and may foster space for evolutionary development by redeeming novel validity. This space may be biochemically assessable by the multiple varying biological functions of, for example, transcription factors [17]. Following modular events, molecular-genetic alterations might occur additionally.

As a holistic process, the therapeutically relevant acquisition of the 'language' of communicative intercellular processes followed by its transformation into a hypothesis-creating activity on the basis of clinical results (derived from modularly designed therapy approaches) may give hints on the 'metabolism' of evolutionary tumor development. Supported by the possibility of redeeming novel validity of communicative processes with modular events, a possible mechanism to promote a tumor's evolutionary development may be simultaneously changing validities of communicative processes mediated by the systems objects. 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 holism of the tumor's living world without first substantially altering the functionality of the entire communicative system.

In analogy to modular therapy approaches, constitutional and incidental modular events from the tumor microenvironment or from the macroenvironment could be critically involved in modularly promoting tumor development or growth. Differentially designed modular therapy approaches should specifically meet a tumor's living world on corresponding steps of tumor development and should allow situation-linked insights in modular architecture (comparative uncovering of a tumor's modular architectures) [27].

Commonly used context-dependent knowledge is shown to underestimate the impact of risk absorbing prepositional background knowledge for pragmatic therapeutic purposes. The combination of modest changes in therapeutic design, i.e. the introduction of biomodulatory therapies, seem to make a major difference in the experimental efficacy of evaluating systems on a communication level.

We may retranslate modularly induced functional changes in tumors into intentional knowledge by comparatively reconstructing novel communication-linked process-

es on a biochemical basis to (1) prove the formal-pragmatic communication theory by an intentional and computational idealization [28, 29], and to (2) advance reductionist knowledge for novel reductionist therapy approaches, which may be used in parallel or subsequentially.

Generally, the new communicatively defined modular coherency of the macroenvironment, i.e. the tumor-associated microenvironment, and the tumor cells open novel ways for the scientific community in ‘translational medicine’.

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## Glossary

Co-option	Reuse of existing genetic components, metabolic reactions, or signaling modules in diverse biological systems, such as tumors, for instance, discharging in the evolution of patterns of dysregulated transcription factors.
Evolvability	The capacity of an organism or a biological system to generate new heritable phenotypes. Therapeutical modularly induced evolutionary steps advance this definition: Modularity may allow retrospectively established spaces for primarily none-heritable evolutionary developments, if modular events (therapy) are implemented.
Modularity	In the present context, modularity is a formal pragmatic communicative systems concept, describing the degree and specificity to which systems objects (cells, pathways, etc.) may be communicatively separated in a virtual continuum and recombined and rededicated to alter the validity and denotation of communication processes in the tumor.
Modular communication (therapies)	The function is to configure the coherence between the validity and denotation of communication

Risk-absorbing background knowledge

Tumor’s living world

processes. Modular therapies may supplement prepositional aspects of communication, i.e. the presence of the tumor’s living world by normative aspects, namely by therapy-derived yes or no statements (‘know that’).

This knowledge constitutes the validity of informative intercellular processes, which is the prerequisite for therapeutic success. Background knowledge about the tumor’s living world is subjected to other conditions of scientific comprehension: Intentional ways fail to describe risk-absorbing knowledge, in which context-dependent knowledge about commonly administered reductionist therapy approaches is rooted. After this second objectifying step (physicians as operators of tumor systems), the network of the holistic communicative activities turns out to be the medium through which the tumor’s living world is mirrored and generated. The living world 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 by implementing the modular knowledge of cellular and external environments (for instance for therapeutic requirements). Only with experimental or therapeutic experiences (modular therapies) is the tumor’s living world separated into categories of knowledge, for example, into modular systems. Specific conditions of compliance for redeeming validity constitute relations between communication technique (specified modular therapy approaches) and distinct tumor-associated situation-engraved systems stages.

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.
Robustness	The inherent property of a system to maintain normal performance despite external and internal perturbations.
Separated or separating 'social' tumor systems	The possibility for redeeming novel validity by modular therapies is indicative for the existence of biologically separated or separating 'social' systems, i.e. in our context, metastatic tumors: Tumors constitute a solitary world with an internal context.

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