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Targeted therapy for neuro-oncology: reviewing the menu

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Targeted therapy against cancer shows not only promise, but also limits. No matter how specific the target, many pathways and cell types can be affected, some unexpectedly. A tumor is heterogeneous and plastic; it can evade a targeting agent or an attack mechanism. Local regulatory factors contribute to site-specific effects. In the brain, widely disseminated tumor, including microscopic tumor; local regulatory differences and impediments to brain-wide delivery can all limit the efficacy of any single agent or approach. Provocatively, precedents for both problems and solutions are seen in the original targeted therapy, the immune response.

Introduction

A fool was very hungry. He ate a loaf of black bread, a herring, a cucumber – at last he was satisfied. ''Ah!,'' he said, ''If only I had eaten that cucumber in the first place.'' A folk tale.

The attack of defined molecular targets is of increasing prominence in cancer therapy [1]. In the idiom of the folk tale, it has taken time to work through the black bread and the herring. Not being fools, we know they had to come first. As we ask what else may be necessary, before we can be satisfied, it is helpful to review the menu that brought us this far.

For tumor outside the brain, targeted therapy has now shown its promise – and its initial limits. The small molecule inhibitor, imatinib (Gleevec), targets the active site of the BCR–ABL fusion protein that is characteristic of chronic myelogenous leukemia (CML). The initial promise was realized when many patients achieved remission. The initial limits are that not all the patients respond and responders can relapse [2–4]. A similar mix of success and limits has been seen with the monoclonal antibody, trastuzumab (herceptin), directed against the epidermal growth factor receptor (EGFR) family member, her2, in her2-overexpressing breast cancer [5]; with monoclonal antibodies and small molecule inhibitors directed against amplified, overexpressed or mutated EGFR family members in other tumors as well [6]; or against the induction of the new blood vessels that support tumor growth (angiogenesis) [7,8]. The greater promise is that, in each case, a wealth of information about the underlying biology aids the analysis of reasons for failure and guides choices about additional or alternative approaches [1–10].

The same approaches – including some of the same targets, agents and insights – are being applied against tumor within the brain [11–14]. There has also been progress with more conventional approaches. The DNA-methylating agent, temozolomide (TMZ), was the first new chemotherapeutic agent to be approved for high-grade glioma in many years [15–17]. Experience with TMZ is directly relevant to newer agents as well. This review brings out choices and insights that have proved important in this evolving work.

The clinical problem

Two kinds of aggressive tumors

(i) Primary brain tumors (tumors that originate within the brain) are the most common solid tumors of childhood [18]. Among all adult tumors, primary brain tumors are rare, but have a disproportionate impact because of their prognosis. The most common and aggressive primary brain tumor in adults is the high-grade glioma, *glioblastoma multiforme* (GBM) [19]. With current therapy, the median survival after the diagnosis of GBM is still less than 15 months [12,14,15,20].

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(ii) Metastases, from tumor that originates outside the brain, are many times more common than primary brain tumors in adults (but rare in children). The most frequent tumors of origin are those of the lung and breast. With conventional therapy, the median survival after the diagnosis of brain metastases is typically measured in months [21–23].

The incidence of brain tumors is increasing. Contributing factors include improved detection and, for metastases, improved control of tumor at other sites [22,24]. A dramatic recent example is seen in breast cancer patients who respond to monoclonal antibody therapy outside the brain, but then show brain metastases [5].

The challenge of treating brain tumors comes from the need to spare function within the brain itself. Although metastasis to the brain is increasingly important, spread from the brain to other organs is rare [25]. In developing new agents and interpreting responses, it is important to take into account the characteristic – and very different – ways that high-grade glioma and metastases become disseminated in the brain (Fig. 1).

Patterns of tumor spread

A defining feature of high-grade glioma (and also seen in lower grade gliomas) is that the tumor does not have a sharp border. Rather, individual tumor cells infiltrate the brain, and are likely to be widely distributed at the time of diagnosis [25–27]. These cells are not readily imaged and, in any case, would be too numerous and widespread to be attacked one-by-one.

Infiltrative glioma originates from within the brain. Metastases, by contrast, enter from the blood (Fig. 1). The number varies with the tumor type and the individual [28]. They can be widely distributed, including micrometastases that are not at first detected [24,26]. In this context, a wide distribution reflects entry at many different vessels, rather than movement through the brain. In fact, for many tumor types, as the metastases begin to grow, they do not actually enter the brain parenchyma. Rather, they grow within, and expand, the perivascular space (PVS). For other tumors, especially lymphoid tumors, metastases may also infiltrate the brain [26]. Infiltrative growth is seen too in primary CNS lymphomas, aggressive tumors seen, not only in AIDS and other immunocompromised patients, but, more rarely, in the general population as well [26].

Tumors can also spread by other routes: tumor can grow along blood vessels, and can be carried in the cerebrospinal fluid (CSF). Metastases can enter, and tumor can spread, in the meninges, the layers of connective tissue that cover the brain [21,25,26].

Thus, for the most common and aggressive tumors, even after the most extensive possible surgery, some form of disseminated tumor is likely to remain. One knows it is likely to be present, but it may be too small to be readily imaged, and too small or too diffuse to be attacked directly. A consequence is that therapeutic agents cannot be delivered directly to all remaining sites, but must instead be delivered more generally. General delivery can be impeded, however, by the blood–brain barrier (BBB), as well as other factors (as discussed below). An equally important problem arises from the volume of brain that must be exposed to potential harmful effects. The conventional therapies – surgery, radiation,

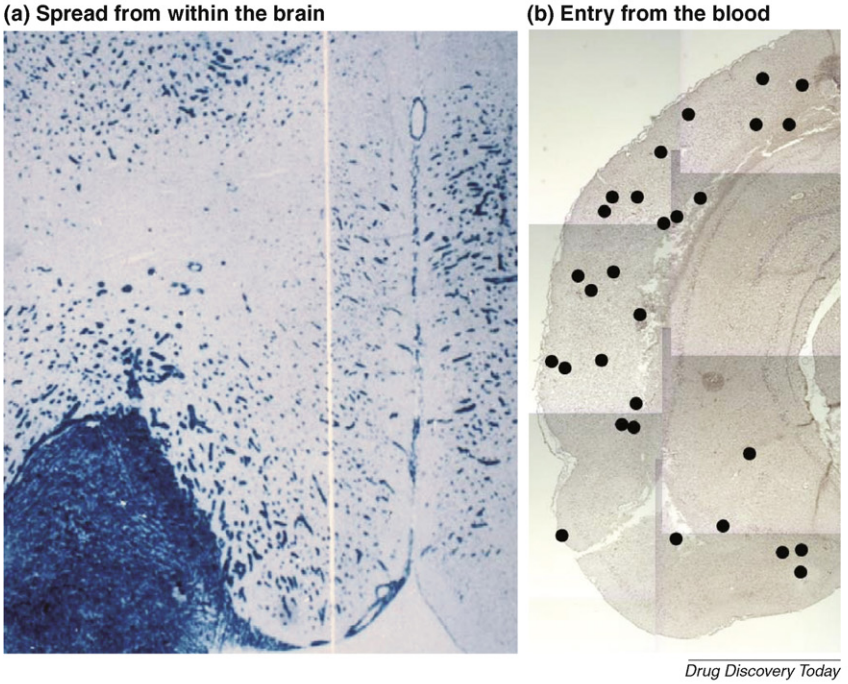

FIGURE 1

Two kinds of tumor dissemination in the brain. **(a)** Spread from within the brain. In a rat model, marked tumor cells, from a gliosarcoma, were implanted in one hemisphere. The tumor (*bright blue*) has formed a mass at the injection site (*at lower left*), and has also spread through the hemisphere and across the midline. **(b)** Entry from the blood. In a complementary rat model, tumor cells, from a mammary carcinoma, were injected into the carotid artery, to favor the delivery of blood-borne tumor to the brain. In this low power overview, *black dots* mark sites where metastases were seen in the brain. At each site, tumor had entered from the blood. Panel (a) adapted from [58].

chemotherapy – are limited by the damage they can cause to functioning brain, each in its own way.

The most aggressive brain tumors can, thus, present two distinct challenges. The existence of previously disseminated tumor means that, even if an initial tumor mass can be removed or controlled, the tumor can recur at distant sites [25,27–30]. Even local therapy is, however, not yet successful. Even for an easily detected tumor mass, residual tumor may remain after surgery or other treatment [20–22,31–33]. Even after aggressive conventional therapy, GBM recurs most often at or near the original site; after radiotherapy, often within the treatment field [20,27,31–33].

There has been sustained effort to improve the efficacy and reduce the toxicity of the conventional therapies. For many years, however, even as understanding of tumor biology increased and methods became more sophisticated, there was little improvement in survival for GBM (as discussed above), and the optimal treatment for metastases remained controversial [28]. Surgery is increasingly sophisticated and safe, but its efficacy is limited by the characteristic growth pattern of many tumors (discussed above), as much as by the need to spare function. Radiation and chemotherapy can increase survival over surgery alone, but, for the most aggressive tumors, the prognoses remained grim and the toxicities limiting. Against this background, regulatory approval of a new chemotherapeutic drug, TMZ, for GBM has had an enormous impact [15–17].

Insights from TMZ

Combinations

TMZ is structurally related to the older alkylating agent, dacarbazine; advantages are that it can be delivered orally and it converts spontaneously from the prodrug to the active form. Although chemotherapy for GBM had been controversial, TMZ has shown efficacy [15–18]. Testing different doses and schedules gave further improvement over the initial trials. After a certain point, however, other ways of increasing efficacy became increasingly attractive [17]. For GBM, a similar point had been reached with respect to radiotherapy and other conventional treatments, as discussed above.

Combining TMZ with radiotherapy did indeed increase efficacy [12,14,15]. Many other combinations, including those with targeted agents, are being tried. Thus, the introduction of one beneficial agent has acted as a catalyst. At the same time, the overall survival advantage of adding TMZ to radiotherapy has been modest [14,15,17,21,31,34], and, indeed, the cost-effectiveness has been questioned [34]. Efforts to build on the initial findings with TMZ, the information and methods used and insights gained, are directly relevant to use of targeted therapy, as discussed below.

Defined mechanism

The way in which DNA-methylating agents, such as TMZ, can kill tumor has been well studied. Equally important, much is known about repair mechanisms that can allow the tumor target to escape [15–18]. These insights affect the use of the drug in many ways. They guide choices about what steps might improve the efficacy of TMZ itself, and what other agents or modalities might be complementary. Equally important, they make it possible to predict which patients will best respond, and which are not likely to benefit. This allows both an individualized approach to therapy and a more meaningful evaluation of efficacy.

These insights depend upon knowledge of both the drug's action and the molecular biology of the tumor. The analysis benefits from a sustained effort to define molecular characteristics of brain tumors [12,19], as well as others. Of course, targeted therapy can benefit from this knowledge base in the same way. In parallel, the ability to test new agents and combinations has been greatly enhanced by evolving methods of clinical trial design and statistical analysis, including re-evaluation of response criteria [7,14,31,35,36].

As important as TMZ has been, there is still a need for more effective agents [15,17,18]. Targeted therapy is being avidly pursued. The text below reviews some of the choices that must be made.

Targeted therapy: selecting the target

The apparent simplicity of a defined molecular target is, upon reflection, deceptive (Table 1). For brain tumors, as for others, the choice of target has implications at many levels. The spectrum of choices, in order of complexity, is considered below.

The molecular target and pathways

At one end of the spectrum is the specific molecular target. Antibodies and small molecule inhibitors that target the BCR–ABL fusion protein, members of the EGFR family, or vascular endothelial growth factor (VEGF) are well-known examples [1–10]. This is just one aspect, however, of target choice.

Further along the spectrum of complexity is the pathway, or set of pathways, that can be affected if the molecular target is attacked. Knowledge of the relevant pathways aids interpretation of results and selection of complementary agents and targets. The situation can, however, be quite complex. It is probable that, for any given molecular target, multiple pathways and multiple cell types can be affected; different effects may either reinforce or contradict each other; and, even for well-studied targets, new functions may be revealed. Some recent examples, among many, illustrate the general point [6,7,37,38].

Certainly, there can be a great discrepancy between functions and cellular targets that are identified – or fail to be identified – in preclinical work, and those that are of major importance *in vivo*, in the human patient. At the same time, the fact that a given

TABLE 1

Targeted therapy: what makes it complex.

Attacking a defined target can have multiple effects
The targeted molecule can affect more than one pathway, in more than one cell type
Once the tumor or vasculature is damaged, many other cells respond
Indirect/secondary/downstream/bystander effects can be beneficial or harmful
The tumor environment is not uniform
The regulatory environment varies from site to site
Disseminated microtumor differs from a large tumor mass
Drug access and efficacy are both affected
The tumor is heterogeneous and plastic
Genetic and regulatory changes continue to occur
The tumor can evade attack
By regulatory changes
By outgrowth of pre-existing subclones
It can evade both the targeting drug and the final effector mechanism

Table summarizes topics discussed in the text.

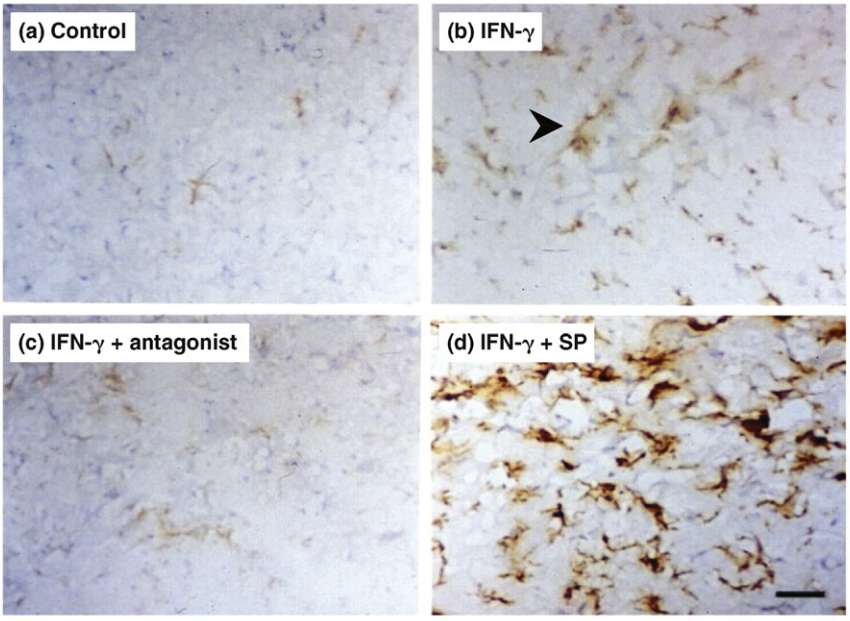

FIGURE 2

Local neurochemicals can affect therapy. The cytokine, gamma-interferon (IFN-γ), can activate microglia throughout the brain. However, the dose required depends on the local environment. One reason is that, in addition to their neurobiological functions, local neurochemicals also modulate other functions. As an example, the figure shows how the neuropeptide, substance P (SP), affects microglial activation in the brainstem, after local injection of a constant dose of IFN-γ. In each panel, activated microglia are *dark brown*. **(a)** Control. There is little activation if only buffer is injected. **(b)** IFN-γ. If IFN-γ is injected, microglia are activated, as compared to control. **(c)** IFN-γ + antagonist. If an antagonist to the receptor for SP is added to the IFN-γ, microglia are no longer activated. **(d)** IFN-γ + SP. If SP is added to the IFN-γ, the activation of microglia is enhanced. Figure adapted from [40].

molecule can serve many functions and affect many cell types is a general principle, seen in many contexts [39,40]. As an example of the general point, in addition to their neurobiological functions, the neurotransmitter, glutamate, and the neuropeptide, substance P (SP) (Fig. 2), can also modulate activation of the characteristic brain phagocytes, the microglia [40]. As a specific example from clinical experience, although EGFR family members are important tumor targets, the family also has essential functions in normal tissue, including the heart and this can contribute to cardiotoxicity when her2$^+$ breast cancer is targeted [5,10].

The cellular target

Even before choosing a molecular target or pathway, it is necessary to select the cell, or cells, that will be the primary focus, and how directly they will be tied to tumor attack. Targeting of molecules such as EGFR family members or the BCR–ABL fusion protein can directly affect the tumor cell. Targeting the tumor vasculature can also affect existing tumor, while targeting endothelial precursors can impede the development of new tumor vessels [13]. Phagocytes have the potential to either enhance or impede tumor growth [41,42]; their migration to the tumor site or their functions could be targeted [41–43]. Still farther afield, targeted therapy could be directed at cells that participate in the antitumor immune response [42].

Secondary effects

No matter how exquisitely specific the molecular target, a complex, interactive cascade of molecular and cellular responses will be initiated if the tumor is successfully attacked. Both endogenous and blood-borne cells can respond to damage of the tumor or vasculature or other changes at the tumor site [41,43].

Looking at these same processes from another angle, they can be seen as contributors to the different kinds of bystander response that are seen with both novel and conventional therapies [41,44,45]. Although bystander effects can contribute to efficacy, they are not necessarily beneficial. Side-effects and toxicities are the negative face of the same phenomenon [46].

How it applies to the brain

To the extent that oncogenes, tumor suppressor genes, signal transduction pathways and stromal effects are common to many tumors [6–8,12,19,41], many targets are shared between brain tumors and others, and many of the same agents can be tested. By contrast, tumor growth, development of vessels, the patient's response to the tumor and the efficacy of a particular therapy can all be affected by the local environment.

As a specific example: the well-studied cytokine, gamma-interferon (IFN-γ), activates phagocytes in many contexts, including microglia throughout the brain. The minimal dose needed, however, differs from site to site. Among other factors, local neurochemicals, such as glutamate or SP (Fig. 2), contribute to the site-specific effects [40]. Thus, even for an agent that is active at many sites, the cellular and extracellular composition of the brain is relevant, as are local differences in the regulatory environment.

Patterns of tumor spread also affect target choice. For GBM, even though infiltrative tumor is likely to be widespread by the time of

diagnosis [25–27], blocking further spread has been of great interest [25]. The presence of infiltrative tumor also affects the expectation for agents intended to block angiogenesis [47,48]. Individual infiltrating cells are well able to use existing vessels, even though angiogenesis may be important for a larger tumor mass. Metastases, in contrast to primary brain tumors, enter from the blood; in that case, blocking initial entry is of interest.

Once a molecular target has been chosen, what agent should be selected to attack it [1]? A small molecule inhibitor? An antibody? A truncated or modified antibody? More indirectly, does one prefer to stimulate an immune response against the target [49]? Many of the considerations apply to tumors at all sites. A special concern for the brain is the role of the BBB.

Reaching the brain

In the normal brain, the BBB prevents the passive entry of antibody and other proteins, as well as many drugs [23,50]. At a tumor site, however, other factors come into play. The normal BBB may be disrupted by the growth of the tumor, further disrupted by radiotherapy or other treatment and lacking in new vessels that form as the tumor grows [21,23,50,51]. By contrast, although a compromised BBB may favor drug entry to a tumor site, other factors impede it: tumor-associated vessels – in any organ – may be leaky, tortuous, chaotic; there can be an unfavorable pressure gradient and changes to the extracellular space can impede diffusion [7,13,52]. Thus, even agents that can cross the BBB may not be well distributed at a tumor site. Paradoxically, efforts to normalize the tumor vasculature may also restore the BBB [47].

The net effect of these different factors on drug delivery for a given patient can be hard to foresee [36,53]. In interpreting clinical findings, different authors have stressed different points. Experience with brain metastases provides specific examples.

Drug delivery to brain metastases

It is often assumed that, because antibodies and many drugs do not cross the normal BBB, systemic delivery of these agents is not appropriate for brain metastases: that the brain is a 'sanctuary site' (as discussed in [23,50,51,54]). From this perspective, it is not surprising when breast cancer patients respond to the monoclonal antibody, trastuzumab, outside the brain, but then show brain metastases, because it is well known that antibody does not cross the normal BBB (as discussed in [5,51]).

By contrast, when brain metastases are detected by extravasation of contrast agents, this implies that the BBB has been compromised [23,24]. From this perspective, brain metastases might be accessible to blood-borne agents after all, even those that do not cross the normal BBB, and agents that are effective outside the brain should be tried against brain metastases as well [50,54].

Taking into account the differences between microscopic tumor and larger masses offers a way to reconcile these two viewpoints (as discussed in [23,50,51]): the BBB may well prevent access to initial micrometastases. As the tumor grows, however, or in response to therapy, the vasculature changes: contrast agents can leave tumor-associated vessels, allowing the tumor to be imaged, and drugs and antibodies may leave as well. According to this model, when patients receiving systemic antibody therapy do develop brain metastases, if the antibody is continued, the tumor may ultimately respond [50].

In sum, agents that can cross the BBB, and methods designed to bypass or open it, are of particular importance for the delivery of therapy to actual or potential sites of microscopic tumor, including infiltrative glioma and micrometastases [23,47,50,51]. For larger masses, the picture is more complex, and not fully understood. The accumulating experience is important for both conventional and targeted therapy [36,47,51,53].

Attacking the target: one is not enough

Having chosen a target, agent and delivery strategy, further challenges are faced at the stage of target attack (Table 1). Tumors are dynamic and acquire new mutations as they grow. A 'tumor' can thus be quite heterogeneous by the time therapy is given and can continue to change. This heterogeneity and plasticity have a major impact on both conventional and targeted therapy.

Attacking a single molecular target may select for pre-existing variants that do not express or depend on it, or may simply elicit regulatory changes that have the same effect. This can occur at the level of a defined molecular sequence or a complex pathway [2–4,6,9,14]. More indirect targeting, such as targeting the vasculature rather than the tumor cell itself, can reduce the problem of tumor evasion, but does not solve it. One reason is that, just as a tumor can evade attack directed against a given molecular target, so can it evade damage by a given effector mechanism [7,13]. The problem is compounded when the tumor takes different forms, such as a large mass plus microscopic tumor, or occurs at different sites, with different regulatory environments.

A logical response to the problem of tumor evasion is to develop a multifaceted attack. The use of alternative agents to attack a given target, attack of more than one target, and combinations of different modalities, including conventional and targeted approaches, are all being exploited [2–4,7,10,13,14,17,31]. In addition to increasing efficacy, combination therapies may reduce toxicity, for example, if the dose of individual components can be reduced. Unfortunately, it is also possible for new or intensified toxicities to appear [5]. Given the many cells and pathways that a single target molecule can affect (as discussed above), this is not surprising. The same knowledge base that guided the initial choice of targeted agents can guide the choice or development of alternatives [5,10].

The original targeted therapy

Parallels to the immune response

Many of the characteristics of targeted therapy have a direct counterpart in the immune response (Table 2). Many of the same determinants can be targeted and, indeed, antibodies are commonly used as targeting agents [1].

Viewed more broadly, exquisite specificity is a hallmark of each. An antigenic determinant is small, just a few amino acids. A given tumor, or even a given protein, can thus present many potential targets [39]. Complementing this, a wealth of effector cells and mechanisms can participate in target attack [55,56]. Thus, the immune response displays the same kind of multifaceted attack that has proved desirable for targeted therapy.

Challenges also have their counterpart in the immune response [55,56]. Corresponding to unexpected harmful effects [5], unexpected cross-reactions and consequent autoimmune disease can

TABLE 2

Two similar menus.

Targeted therapy	*Immune response*[a]
Well-defined molecular targets	Well-defined molecular targets
Need multiple targets	Many antigens recognized
Many agents per target desirable	Per antigen, many effectors stimulated
Combined modalities beneficial	Many effector mechanisms contribute
Secondary/bystander effects	Response an unfolding cascade
BBB can impede passive delivery	BBB blocks antibody
May see unexpected toxicities	May see mis-regulation, autoimmunity
Tumor can escape	Tumor can escape
A la carte menu	Tasting menu, prix fixe
Components chosen by investigator	*Multi-faceted by default*

[a] Properties of the immune response are reviewed in [55–57].

occur. Anticipating the growing interest in feedback loops [11], an unfavorable immuno-regulatory balance can cause problems that range from lack of efficacy to an overexuberant response which, especially in the brain, can be as harmful as the tumor itself.

Being aware of these parallels may contribute to solving some problems, and foreseeing others. For example, the BBB impedes passive entry of antibody in both responses, but antibody-forming cells can cross it [57]. More sobering is that, despite its multifaceted heterogeneity, tumors can still evade immune attack [42].

Conclusion: anticipating the final course

In the menu of advantages and complexities of targeted therapy, the parallels to the immune response are striking (Table 2). Targeted therapy has now shown its promise; the complexities are still being revealed. The promise of immunotherapy is older, and new complexities are still being revealed. As the two approaches evolve, exploiting many of the same methods, knowledge and insights, it is intriguing to consider which will satisfy us first – and if it will still be possible to tell them apart.

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