Informing materials: Drugs as tools for exploring cancer mechanisms and pathways

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Abstract

This paper builds on previous work that investigated anticancer drugs as 'informed materials', i.e., substances that undergo an informational enrichment that situates them in a dense relational web of qualifications and measurements generated by clinical experiments and clinical trials. The paper analyzes the recent transformation of anticancer drugs from 'informed' to 'informing material'. Briefly put: in the post-genomic era, anti-cancer drugs have become instruments for the production of new biological, pathological, and therapeutic insights into the underlying etiology and evolution of cancer. Genomic platforms characterize individual patients' tumors based on their mutational landscapes. As part of this new approach, drugs targeting specific mutations transcend informational enrichment to become tools for informing (and destabilizing) their targets, while also problematizing the very notion of a 'target'. In other words, they have become tools for the exploration of cancer pathways and mechanisms. While several studies in the philosophy and history of biomedicine have called attention to the heuristic relevance and experimental use of drugs, few have investigated concrete instances of this role of drugs in clinical research.

Keywords

Oncology. Anti-cancer drugs. Targeted therapies. Cancer genomics. Next-generation sequencing. Clinical research.

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Introduction

This paper examines a fundamental reconfiguration of the use and meaning of anticancer drugs in the post-genomic era by focusing on their transformation from 'informed' to 'informing materials'. The notion of 'informed material' (Cambrosio et al. 2012), refers to the fact that during development and post-marketing stages, drugs undergo 'informational enrichment' (Barry 2005; see also Gomart 2002) in a dense web of qualifications and measurements that spans the entire spectrum of oncology research and practice. Kimmelman (2012), from a bioethical perspective, has coined the somewhat germane term of 'intervention ensemble' to refer to the "coordinated set of materials, practices and constraints needed to safely unlock the therapeutic or preventive activities of drugs, biologics and diagnostics." Erring on the side of epistemology rather than bioethics, the notion of informational enrichment highlights the relational nature of drugs and the fact that they exhibit emerging properties derived: (a) from their progressive involvement in clinical experimental systems and models; and (b) from comparisons and combinations with other drugs within distinct regulatory settings, to whose redefinition they contribute (see also Gillick 2014; Pieters 2005). This notion contrasts sharply with the idea that the properties and characteristics of a given compound, such as their safety and efficacy, are intrinsic qualities of that substance. It thus also contradicts the notion that a substance retains its biochemical, pharmacological, and therapeutic identities throughout the sequence of drug-making, drug-testing, and drug-using practices that defines its biomedical and regulatory trajectory.

The key claim of our paper is that while they maintain their status of informed material, anti-cancer drugs in clinical trials have more recently become tools for analyzing their targets or, put differently, instruments for exploring cancer pathways and mechanisms that lead to new biological, pathological, and therapeutic insights into the etiology and evolution of cancer. In short, they have become 'informing materials'. Needless to say, this recent development is not purely conceptual; it has already led to a marked transformation of the organizational arrangements for pursuing cancer clinical research. Institutional translations of this trend include, for instance, the establishment of research and treatment centers for 'mechanism-based therapy' where drugs are used to explore and intervene on molecular oncogenesis processes. This trend has also led to an increasing permeability of the boundary separating research from care. As detailed in the next section, these developments parallel the redefinition of the therapeutic toolbox from cytotoxic chemotherapies to targeted therapies, i.e., from indiscriminate cell-killing to targeting specific molecular abnormalities of tumor cells, such as specific

mutations that drive cancer growth. As increasingly sophisticated generations of these new drugs reach the clinical testing stage, they add up to a diversified and robust collection of tools that enable the dissection of cancer cells' signaling networks.

Before exploring specific examples of the alternating role of drugs as informed and informing materials, we need to confront a possible objection, namely that there is nothing new in our claim, since drugs have been used as 'informing material' for decades. In particular, critics of our argument have mentioned research on psychiatric disorders in the late 1950s, when psychotropic drugs led to the establishment of a correlation between monoamine metabolism and depression. Building on these initial insights into the biology of depression, investigators pursued research of antidepressants, which they saw as providing them "with powerful tools for exploring the biochemical changes that may be associated with these disorders" (Schildkraut 1970, p. 136). Similarly, in his analysis of research on schizophrenia, Tsou (2012) highlighted the "importance of pharmacological drugs as research tools in the generation of psychiatric knowledge and the dynamic relationship between practical and theoretical contexts in psychiatry." And yet, the use of psychotropic drugs as research tools has also been widely criticized—both by social scientists and by contemporary neuroscientist—for its lack of correlation with specific pathogenic events. For instance, in their review of the biological insights provided by antidepressants, Krishnan and Nestler (2010, pp. 1306-8) argue that "currently available agents likely restore mood by modulating distinct processes that are unrelated to the primary pathology of depression."

This points to a fundamental difference between psychiatry and other, somatic biomedical domains such as oncology, which has important consequences for our argument about drugs as informing materials. Because of the "weakness of the association between genes and psychiatric disorders," Mitchell (2009) is skeptical about "the kinds of knowledge one should expect to glean from such [genetic psychiatry] studies." Psychiatric disorders show "features of complex systems" and are characterized by the "variability of causal pathways and multiplicity of contingent factors." Whatever epistemic signals drug responses produce in psychiatry, they are undermined by the complexity of mental illnesses. While similar claims are not totally absent from the field of oncology, the degree to which specific drug-based tools—'targeted therapies' but also related diagnostic, prognostic, and predictive biomarkers—provide measureable insights about bio-pathological mechanisms is unprecedented. It stands in sharp contrast with the generic mechanisms explored in psychiatry or by early cancer chemotherapy drugs (see next section). While one could argue that this is only a matter of degrees, we maintain that it represents a qualitative leap. As noted by Lakoff (2006) in his analysis of 'pharmaceutical reason', in psychiatry the "adjustment between the drug's effects and the characteristics of its target population is not due to the development of more directly targeted drugs," as is the case in oncology. Rather, the "adjustment process occurs at the diagnostic level. The drug remains stable while the target shifts in relation to it. … The model is in a sense being *made* more accurate, not

by finding the perfect pharmacological key to fit the illness but by changing the very nature of the lock into that which, by definition, matches the key." As we will show, recent cancer research exemplifies the presence of qualitatively different processes.

In the remainder of this paper, we will analyze a few key examples that we have identified as part of a broader research project on cancer genomics that deploys a three-pronged ethnographic approach consisting of: (a) the systematic collection and analysis of published and unpublished documents (scientific articles, company reports, web newsletters and blogs); (b) interviews with cancer clinicians, researchers, statisticians and the staff of biotech companies on both sides of the Atlantic; and (c) participant-observation at scientific meetings and within clinical settings (in the US, Canada and France). As part of this fieldwork we regularly encountered material directly related to the topic of this paper, and we were thus able to extract relevant information from our notes and interviews. In our concluding remarks, we will return to the implications of our argument about the use of drugs as informing materials, not only, and most obviously, for those interested in the epistemic dimensions of biomedical research, but also for scholars in science studies working on the social dynamics of pharmaceuticals.

From informed to informing materials

As detailed in Cambrosio et al. (2012), informational enrichment in oncology has been typically pursued through clinical experiments that articulate tumors, defined by organ and tissue of origin (breast cancer, lung cancer, etc.), and drugs (individually, or as part of combination regimens) in an array of correlations. Two major, related events have modified the landscape in the last 15 years. The first is the development of high-throughput technologies, epitomized by next-generation sequencing (NGS). Genomic sequencing methods allow clinical researchers to characterize patients' tumors based on the genetic mutations they harbor, rather than the organ of origin and stage of development (Nelson et al. 2013). This has precipitated calls to move oncology 'beyond histology' (e.g., Meador 2014), given that insofar as cancer is now a 'disease of DNA', mutations are what matters. This claim remains controversial, however, as the 'same' mutations in different organs behave and react to treatment differently; in other words, "context [still] matters" (e.g., Horlings et al 2015). And yet, it is undisputable that all major cancers have of late undergone a process of fragmentation that has replaced common diseases with a growing number of rare diseases, each defined by a combination of genetic and genomic biomarkers (see Harbeck and Rody 2012, p. 688, for a telling illustration of this process in the case of breast cancer). The fragmentation process, moreover, is not only contingent on the presence of distinct mutations (or combinations thereof), but also on the differential reaction of the new disease entities to specific kinds of targeted treatments that also have dramatically increased. While the chemotherapy toolbox of the past century contained only a few dozen drugs, a large number of innovative drugs have been approved since the turn of the new century, and more than 800 substances have reached the clinical testing stage (PhRma 2015, IMS 2016). Most of these substances are deemed 'targeted therapies' insofar as they target specific mutations and pathways, rather than generic cell cycle mechanisms.

The initial understanding of anti-cancer drug action was based on early insights into cell division and the biosynthesis of nucleic acids. Figure 1 summarizes knowledge of the mechanisms of chemotherapy circa 1969. Researchers in the 1950s had hypothesized that substances that disrupted these processes would damage rapidly proliferating tumor tissue more than the relatively stable healthy tissue. This principle remains current and the research associated with cytotoxic therapeutic practices has therefore concentrated on the modalities of dosage, combining agents, and elucidating the details of drug action on human metabolism. This is not to say that clinical research conducted prior to the present era was merely empirical. Trialists themselves believed that their work contributed to the elucidation of disease mechanism (e.g., Ravdin 1960). Differences in sensitivity to cytotoxic treatment reported by trials were often claimed to be a basis for exploring "underlying biological differences" in cancers (Keating and Cambrosio 2012, p. 188). Nonetheless, despite these claims, the U.S. National Cancer Institute regularly pressed the US cooperative oncology groups (the public network of clinical trialists) to collaborate more closely with academic medicine to increase the experimental import of trials, and routinely charged that oncology trials lacked science (Keating and Cambrosio 2012, p. 351). More recently, critics have similarly argued that clinical research since the 1960s has contributed little to further understanding of mitosis (cell division): a 2005 review of advances in mitosis inhibition, for example, admitted that "the mechanism linking long-term mitotic arrest to cell death has remained almost completely unexplored" (Weaver and Cleveland 2005, p. 7).

FIGURE 1 APPROX. HERE

We leave aside the debate as to the extent to which the recent developments in the field of genomics should be qualified as 'disruptive', as many, including grant agencies, believe they should, or whether such developments—given their necessary articulation with established clinical practices (Kohli-Laven et al. 2011)—are better understood as components of more mundane activities, as others have argued. [1] In either event, they have clearly contributed to an experimental turn in clinical cancer research. In particular, the informational enrichment of anticancer drugs is now played out in a relational space of information about a drug's molecular targets and mechanisms of action, competing treatment regimens, and molecular characterizations of tumors. In short, in current clinical cancer research, the understanding of drug action and of cancer biology advance together.

As the term 'precision medicine' suggests, much of the power of recent genomic technologies and of the drugs that have been designed on that basis has been ascribed to their capacity to select specific molecular targets. Yet, almost paradoxically, one major implication of these developments is a destabilization of the concept of 'drug

[1] See, e.g., http://www.genomecanada.ca/en/programs/leading-edge-technologies/past-competitions/2015-disruptive-innovation-genomics-competition

target' that has been so central to biomedical innovation since Paul Ehrlich introduced the 'magic bullet' metaphor at the dawn of the past century (Silverstein 2002). Indeed, the 'lock-and-key' metaphor that underpins many mechanistic explanations of drug action is increasingly unable to grasp the complex biopathological processes revealed by drug-driven clinical experimentation. As we will see below, the evolutionary models through which tumor development and drug action are now understood include a number of flexible and changing pathways populated by often-interchangeable cellular entities and processes. Drug intervention on these processes provokes both stable and unstable rearrangements of the pathways and the genes and proteins involved in them – it does not simply block or eliminate a disease mechanism. In other words, drugs used as informing materials have problematized the concept of 'drug target'.

Expanding (onco)genes through drugs

The 'expansion' of an oncogene known as RAS (Atreya et al. 2015) provides us with an example of our claim concerning the destabilization of targets. Established in the early 1980s, and positing that malignant transformation is induced by genetic material already present in the cells (the 'enemy within'), the 'oncogene paradigm' (Morange 1997, 1993) inaugurated the modern era of cancer research. A 1988 review of the burgeoning field concluded: "we now understand that normal control of growth, development, and differentiation is determined by molecular genetic mechanisms residing ultimately in the cellular DNA" and that "the oncogene concept provides us with a reasonable molecular 'handle' with which to deal with cancer" (Burck et al. 1988, p. 279). The following year, another review of the field opted to focus on "selected oncogene systems that showed promising clinical relevance: the *myc* and *ras* oncogene families" (Benz and Liu 1989, p. viii). By 2011, yet additional reviewers observed that because of its implication in both pathological (cancer) and physiological processes, the RAS oncogene family had been "very extensively studied over the [previous] 3 decades, with more than 40,000 scientific articles published on the subject during this period," and that it still commanded 200 to 300 new publications per month (Fernández-Medarde and Santos 2011, p. 344; see also Malumbres and Barbacid, 2003).

How does this relate to drugs? Members of the RAS family include a gene known as KRAS that played a prominent role in the development of targeted therapies. Early examples of successfully marketed targeted drugs include gefitinib, erlotinib, and cetuximab, three inhibitors of a cell surface molecule known as EGFR (Epidermal Growth Factor Receptor), which activates a cascade of other molecules that transmits signals from the cell surface through the cell to the DNA in the cell nucleus, thereby regulating processes such as cell differentiation, proliferation, or death. A signaling cascade is known as a pathway, a major example of which is the MAPK/ERK pathway of which RAS is a component. To further complicate things, pathways are interconnected, with the RAS family acting as a node linking different pathways, and thus qualifying as a "star player" in carcinogenesis (Pecorino 2012, p. 16). Figure 2, which can be usefully contrasted with Figure 1, illustrates the kind of mechanism-based understanding that characterizes recent work on cancer pathways. Retrospective analysis of clinical trials of

anti-EGFR therapy showed that only those patients who had the wild-type (i.e., non-mutated) KRAS gene responded to therapy (Karapetis et al. 2008). Subsequent guidelines for anti-EGFR therapy included the requirement to test the mutational status of KRAS (e.g., Allegra et al. 2009). Genes such as RAS, however, are complex entities that consist of a number of genomic regions (namely exons and introns, referring respectively to coding and non-coding regions, and codons, i.e., subcomponents of exons), only some of which were initially known to harbor mutations that conferred resistance to targeted therapies. Following a "bounty of secondary analyses of phase II to III clinical trials" (Atreya et al. 2015, p. 682), however, a number of unknown mutations in other regions of the gene came to light creating a situation described as 'expanded RAS'.

FIGURE 2 APPROX. HERE

Thus, while the initial work that led to the emergence of a RAS oncogene model used more traditional laboratory and pre-clinical approaches (Malumbres and Barbacid 2003; Karnoub and Weinberg 2008), recent contributions to the functional analysis of RAS have been made through clinical trials with targeted agents. These trials have "expand(ed) the RAS genes" by producing signals of functional relevance in previously unexplored exons. Clinical trials of anti-EGFR agents showed that subsets of patients with no response to wild-type KRAS harbored less common, mutated exons that had been overlooked. Moreover, in addition to an expanded list of KRAS codons, expanded RAS also added mutations in NRAS (another member of the RAS family) that appear to be mutually exclusive of KRAS mutations (Atreya et al. 2015). The mechanisms through which these tumors resist anti-EGFR therapy have also been actively explored, with findings showing how mutationally differentiated populations of tumor cells can "transmit" drug resistance from one population to another (e.g., Salazar et al. 2014). While the purpose of these investigations was to refine patient populations for treatment-related purposes, and thus to improve the informational enrichment of drugs, initial observations on drug resistance have led researchers to simultaneously identify novel features of cancer biopathology—in this case: of the detailed molecular anatomy of an oncogene and related pathways—with the drugs used thus acting as informing material.

Stratification and experiment: Crizotinib and ALK

Clinical trials of targeted therapies stratify patients according to the molecular abnormalities displayed by their tumors. One of the main objectives of these trials is the collection of tumor tissue samples, a critical resource that, combined with clinical annotations, is used for follow-up investigations of molecular pathways (Nelson et al. 2014). In turn, new molecular insights have led to a revision of the nosology of cancer. This approach is exemplified by work on another oncogene known as ALK (for anaplastic lymphoma kinase). ALK alterations were initially identified against a background of uneven responses to the aforementioned EGFR inhibitors in clinical trials, prompting a search for unknown mutations of therapeutic significance (Ou et al. 2012). For the 5-7%

of patients with a form of lung cancer defined by the fusion of the ALK and EML4 genes, a number of therapeutic options have emerged, turning the target/drug 'match' between ALK and a drug known as crizotinib into one of the poster children of personalized medicine (Gillick 2014). The presence of molecular alterations and the response to drugs targeting them is now used to establish novel subtypes of lung cancer. A review of crizotinib and the EML4-ALK translocation captured the essence of the argument with the crisp title: "Crizotinib: a drug that crystallizes a unique molecular subset of non-small-cell lung cancer" (Ou 2012). The title makes it amply clear how the drug functioned as the experimental instrument that established the new molecular subtypes of this cancer histology. A related paper went even further by describing crizotinib as what Latour (2005) would call an actant, insofar as this substance has not only "changed the paradigm of future drug development for targeted therapies by targeting a molecular-defined subtype of NSCLC despite its rarity," but also "affected the practice of personalized medicine in oncology, emphasizing close collaboration between clinical oncologists, pathologists, and translational scientists" (Ou et al. 2012, p. 1351). It thus appears that the stratification of patients according to predictive mutational biomarkers has consequences—encompassed under the term 'precision medicine'—for a number of connected domains, such as nosology, treatment protocols, prognosis, professional guidelines for clinical practice, and regulatory decisions.

The results of the investigation of the ALK-crizotinib connection have stimulated new hypotheses about the transformation of cancer pathways. For instance, different molecular subtypes are assessed and compared for their histologic, cyto-morphologic, and clinical features (e.g., Nishino et al. 2012). These features are then traced back to the biopathological pathways affected by the specific mutational configuration of those tumors. In this way, 'mechanistic insights' into the ALK mutations, including those gained in clinical trials of experimental agents, participate in the elucidation of the core mechanisms of oncogenesis (Hallberg and Palmer 2013). In addition, drugs confirmed to target a given mutation through the analysis of trial data may also be used to identify other mutations. Clinical research exploring the Crizotinib-ALK relation has led to the investigation of the functional role of alterations of a proto-oncogene known as ROS1. Comparison of responses with the data already collected for ALK "suggest[ed] that ROS1 rearrangement defines another unique molecularly defined subtype of lung cancer with heterogeneity." Subsequent research, recently sanctioned by the FDA (ASCO Post 2016), confirmed the hypothesis, initially reached through inference and analogy, that crizotinib also targeted tumors with ROS1. This demonstration was then used as a proof of principle that the ROS1 rearrangement also drives cancer progression in those tumors (Ou et al. 2012). In other words, the prior informational enrichment of crizotinib in terms of the response of tumors in a certain subtype (ALK) now allows responses observed with this drug to function as a tool for validating new mutational subtypes of lung cancer. The ALK-crizotinib system acted, in other words, as a material and conceptual model for research on other biomedical objects, and provided a roadmap for innovative follow-up experiments (see Creager 2001, p. 328; Rader 2004, p. 14).

Evolutionary approaches and mutational landscapes

Moving from a static to a dynamic understanding of oncogenesis, recent approaches model the development of cancer as a sequence of phylogenetic events shaped by evolutionary pressures exerted, in particular, by drug action (Klein 2013; Vogelstein et al. 2013; Swanton 2014). Oncologists, sadly aware that many patients relapse after initial tumor regression due to the gradual development of resistance to therapy, have long known that tumors evolve in response to treatment. No clear understanding of these phenomena, however, was available, and evolutionary approaches to cancer remained an interesting general hypothesis, rather than a direct contributor to treatment (Greaves 2001; 2015). As a clinical researcher noted, "we used to say to patients all the time that cancers are evolving in a Darwinian manner, but we didn't have a huge amount of evidence at our disposal to really formally prove that" (Swanton, cited in Willyard 2016, p. 166). The development of advanced molecular tools, in parallel with initiatives such as the Cancer Genome Atlas, launched in 2005, shed new light on the situation. Using recently available sequencing technologies, and by analogy with 'evolutionary landscapes', researchers introduced the metaphor of 'mutational landscapes' to refer to the recurring set of mutations that drive different types of cancer (e.g., Kandoth et al. 2013).[2] Related metaphors such as 'mutation burden' or 'load' have also become commonplace. On this basis, it became possible to show that, far from being constituted by identical cells, tumors show varying degrees of intra-tumor heterogeneity, i.e., they harbor several distinct cell populations driven by different mutations. Similar to the mechanisms of natural selection, chemotherapy drugs, by preferentially killing certain cell populations, favor the development of other, resistant populations (Willyard 2016). As succinctly stated by a leading researcher in this domain, "I started my journey believing that we were up against oncogenes, but what we need to defeat is evolution" (fieldnotes, MAP 2015 conference). Drug resistance, in other words, has become linked to the (clonal) evolution of cancer cell populations, and in return drugs have become a tool for studying mechanisms of clonal evolution.

Compared to traditional chemotherapy, targeted therapies directed against specific mutations that drive the dominant clone are, at least in principle, a sharper tool for exploring clonal evolution. The development of targeted agents allows researchers to exert some control over tumor evolution and make it amenable to experimental manipulation. Studies of drug resistance have led to the investigation of the "remarkable metabolic flexibility of tumor cells" and the properties of the biopathological pathways at the heart of cancer generation and propagation (Ramos and Bentires-Alj 2015, p. 7). In this regard, research on resistance-sensitive regimens is now less the study of treatment failure than the study of 'therapy-induced cancer biopathology'. Discussing the case of a patient who was the subject of detailed investigations following an intriguing drug response, the Physician-in-Chief and Chief

[2] Analogies with the field of evolution have become common: for a somewhat extreme example see Walther et al (2015). For a philosopher's critical assessment of evolutionary accounts of cancer, see Germain (2012).

Medical Officer of the Memorial Sloan Kettering Cancer Center characterized this series of experiments as "pure Darwinism," adding that "it's a remarkable story of tumor evolution. I mean can you imagine if Darwin would be alive today? Instead of finches [the birds Darwin collected on the Galapagos islands], he would be looking at the evolution of the genomic landscapes of tumors, and he would be in paradise" (Interview with José Baselga, November 2014).

In the UK, researchers have established a clinical trial program with the catchy and revealing acronym DARWIN (Deciphering Anti-tumour Response With Intratumour Heterogeneity). They hope that a better understanding of both the spatial and temporal dynamics of heterogeneity will not only result in therapeutic insights, but also have consequences for clinical trial design, which will in turn provide additional evidence concerning clonal evolution (Hiley et al. 2014). Part of the DARWIN program, a lung cancer study called TRACERx (TRAcking non- small cell lung Cancer Evolution through therapy [Rx]), involves "following cancers from diagnosis to relapse, tracking the evolutionary trajectories of tumours in relation to therapeutic intervention" (Jamal-Hanjani et al. 2014). In this regard, drugs act as a signal-generating instrument for the exploration of the development of cancer (in particular, the processes leading to the acquisition of resistance), and, in return, lead to the attempt to define, on this basis, "a new process for drug development" (Jamal-Hanjani et al. 2014), i.e., one leading to a different kind of informational enrichment.[3] As explained by a member of the DARWIN team (interview with Crispin Hiley, January 2016):

> Say that we could understand the biology better, so we could understand the effect of tumour heterogeneity, and along with biopsies pre and post, the effect of evolution on how resistance might develop, and what might enable that resistance. And we are also hoping that it would give us an idea about class effects. So, if we use vemurafenib [a BRAF inhibitor], it would still tell us about what would happen if you had debrafenib, which is another BRAF inhibitor. These trials are not done because we're only ultimately interested in vemurafenib, in the drug itself. We're interested in BRAF inhibition in non-small cell lung cancer, and how tumour heterogeneity affects that.

Exceptional responders and basket trials

We have so far shown how targeted agents have become full-fledged experimental tools, or, to use the term we propose here, informing materials. We have yet to discuss, however, how this stands in relation to another key feature of anticancer drugs, namely their character as informed material. While, as already mentioned, informational enrichment is a long-standing feature of therapeutic practice in oncology (Keating and Cambrosio 2012), it has been reframed following the new-found experimental capacity

[3] The ensuing organizational changes for clinical research systems are far from trivial (Ramos and Bentires-Alj 2015). There has been in recent years a proliferation of proposals and initiatives for developing innovative clinical trial designs and infrastructures.

of drugs to target specific molecules and pathways. The conclusion of the previous section suggested that in recent years, informational enrichment and the use of drugs as informing materials have become but two sides of the same coin. The 'exceptional responders' program provides an illustration of this process, and highlights the organizational changes occasioned by the transformation of drugs into experimental tools.

Exceptional responders are patients (usually participants in clinical trials) whose tumors had strong, durable responses to an agent that otherwise failed to increase survival or produce responses in most other patients. Clinical trials of such agents were considered failures, and the very few positive responses treated as statistical noise (Sheridan 2014). In the world of mechanism-based therapy inaugurated by the development of targeted agents, however, statistical noise has been turned into a signal and a possible niche market for otherwise failed drugs. In other words, tumor response to anticancer drugs in a single patient has become a potentially robust signal produced by the underlying genomic features of that patient tumor's singular mutational landscape. The transformation of statistical outliers into valuable experimental subjects is emblematic of the changes introduced by the combination of targeted agents and sequencing, and of its present and potential consequences for clinical trials, the keystone of clinical cancer research.

Sponsored by the US National Cancer Institute, the main objective of the Exceptional Responders initiative is to "understand the molecular underpinnings of exceptional responses to treatment."[4] The initiative includes amongst its early advocates two oncologists from the Memorial Sloan-Kettering Cancer Center in New York, David Solit and Charles Sawyers (Sawyers was a key actor in the development of imatinib, still the most successful example of targeted therapy). Both researchers are housed in the 23-story, state-of-the-art Zuckerman Research Center, where Solit leads the recently established Center for Molecular Oncology (CMO), made possible by a 100 M$ gift from billionaire philanthropists Henry and Marie-Josée Kravis. The CMO collaborates with the MSK Center for mechanism-based therapies, which Solit has described as the "effector arm" of the CMO (Solit interview, November 2014). The Physician-in-Chief of the MSKCC described their "mechanism-based" approach as seeking to understand the molecular pathways driving cancer development that begins by proactively contacting pharmaceutical companies with drugs inhibiting certain pathways and moving the drugs of interest into clinical trials (Nelson et al. 2014, p. 76).

Solit's laboratory had done the whole genome analysis and other correlative studies for a clinical trial of a drug called everolimus that targets the protein products of the mTOR gene. The drug was administered to patients with cancers known to be driven by mTOR aberrations. The trial was unsuccessful, but one patient showed a complete response and subsequent analysis of the tumor tissue revealed that another gene had to be

[4] http://www.cancer.gov/news-events/press-releases/2014/ExceptionalRespondersQandA

mutated in order for the mTOR pathway to become a tumor driver. Published in *Science* (Iyer et al. 2012), these results drew much attention. Solit has explained his general approach in the following terms:

> We take patients who have already responded to a drug, but we didn't quite understand the biology there, we didn't have a known biomarker that predicted for that response, and we now profile them, figure out what that known marker is, and then try to do an iterative study where we enroll patients with that biomarker to ask how often do patients with that particular mutation respond… We know the drug could hit the target because this individual responded, and if we could figure out what made them genetically unique, maybe there are other patients just like them for which we already have a good drug sitting on the shelf. (Interview, November 2014)

Solit's starting point, therefore, was the unexpected drug-tumor response relation obtained from a previous trial, which provided the relevant experimental signal. This signal was subsequently treated as a fixed parameter and used to establish a 'clinical experimental system' (Rheinberger 1997; Nelson et al. 2014) in order to identify a new epistemic object, i.e., the hitherto unknown mutation and its functions that account for the experimental signal, using deep sequencing as the technology of choice.

Based on the results obtained from the sequencing of the exceptional responders' tumor tissue, and building on the data stored in online archives of known mutations and pathways, investigators currently hope to establish a molecular hypothesis that will relate the drug-response signal to a biopathological pathway. As a NCI team noted, drug response will be correlated with molecular hypotheses and biopathological models, and "molecular features identified will be classified into known cancer pathways with potential therapeutic relevance, and these data will be correlated with the putative mechanism of action of the therapeutic agent that the patient received" (Takebe et al. 2015, p. 2).

The investigation of exceptional responders has been characterized as a P2G approach (phenotype to genotype), its mirror image being the G2P approach. In both cases the issue is to relate drug signals, mutations, and pathways, but the sequence is inverted. Innovative approaches in oncology clinical trials that adopt a G2P approach include so-called 'basket trials'. In contrast with 'umbrella trials' that test a number of different drugs, each targeting a different molecular alteration, in patients with a same type of organ-defined tumor (say: lung cancer), basket trials enroll patients with a range of different tumor types that share a same mutation. Basket trials, in other words, are based on the supposition that "a lung tumor and a breast tumor with inappropriate activation of the same signaling pathways may share more molecular vulnerabilities with each other than with a lung or breast tumor lacking the same mutations" (Redig

and Jänne 2015, p. 1). A highly cited Phase-2 basket trial of a drug called vemurafenib (Hyman et al. 2015) provides a clear example of this kind of trial. Initially developed in patients suffering from skin tumors (melanoma) bearing a BRAF V600 mutation, the drug was used to treat a total of 122 patients with different types of BRAF V600 mutation–positive cancers with results that led clinicians to conclude that "*BRAF* V600 appears to be a targetable oncogene in some, but not all, nonmelanoma cancers" (p. 726).[5]

Obviously, compared to clinical trials such as TRACERx that are closer to the experimental pole of the translational research spectrum, basket trials tend towards the therapeutic end of the spectrum since their defined aim remains to develop effective therapies. And yet, basket trials also represent crucial tests for molecular hypotheses insofar as they establish an experimental context within which drug response can be related to a specific molecular abnormality beyond the boundaries of single organs. A number of variations have emerged with respect to this kind of clinical trial design. In addition to an explicit call for combining umbrella and basket trials (Klauschen et al. 2014), we should mention here a major trial sponsored by the NCI. Called NCI-MATCH, and treating patients from across 2,400 US sites, this trial can be characterized as an umbrella protocol for multiple, single-arm basket trials, as it consists of a number of studies, each focusing on a different molecular alteration and targeted treatment (of which more than 20 will be tested). NCI-MATCH is close to the therapeutic and regulatory end of the translational research spectrum, insofar as several of its components are 'locked down' in order to ensure reproducibility. For instance, treatment is assigned by algorithm and not by discussions among the participating physicians, and next-generation sequencing using a standardized panel is carried out in a few, select centers. One of the criticisms of the trial is that it appears to test the feasibility and logistics of molecular sampling across a large number of different institutions, rather than testing clinical hypotheses. As noted by one interviewee who prefers to remain anonymous:

> What is the primary endpoint of [the NCI-MATCH] study? Is the primary endpoint of the study to show that genotyping is feasible? Or is the primary endpoint of the study to answer the question does this drug induce a response when you have this particular mutation? … If the purpose of the MATCH trial is to show that they can do centralized testing and get biopsies on patients with advanced cancer, that's great. But that's not what I'm interested in.

And yet, one could argue that NCI-MATCH also provides an experimental context within which drug response data can be related to specific molecular abnormalities within a

[5] The Web of Science defined the resulting publication as both a "hot paper" (a paper published in the past two years that received enough citations to place it in the top 0.1% of papers in the academic field of Clinical Medicine), and a "highly cited paper" (as "it received enough citations to place it in the top 1% of the academic field of Clinical Medicine based on a highly cited threshold for the field and publication year").

single protocol, thus superimposing the relational spaces of drugs, therapeutic regimens, and patient subpopulations on the space of mutational landscapes. Interestingly, during a 2013 presentation of the trial design in front of the National Cancer Advisory Board, one of the trial designers reacted to criticism that each of the sub-studies was too small to produce statistically robust results, by specifying that the trial was a "signal-finding trial," i.e., one that looked across tumors to see whether treating by molecular characteristics, regardless of the tumor, was effective (NCAB 2013, p. 15), a qualification more recently confirmed by the director of the Division of Cancer Treatment and Diagnosis and NCI deputy director for clinical and translational research (Anonymous 2017, p. 8).

To sum up, situating drugs in reference to new trial designs shows that they can occupy a number of different positions. Early phase trials with the more traditional goal of generating toxicity and safety data contribute to the informational enrichment of new drugs. In the case of more experimental or exploratory genomic-driven trials, while engaging in their own informational enrichment process—e.g., by relating drug response to a molecularly stratified patient population—drugs also act as informing material. They do so, for instance, by provoking exceptional responses that can subsequently be explored by correlating these responses to a drug's purported mechanism of action, or by eliciting different responses from the same mutation in a variety of tumors types, thus leading to the investigation of the relation of mutations to a tumor's histology. In other words, when clinical trials, in combination with laboratory and pre-clinical experiments, resort to sequencing technologies to gather information on the mutational landscape of a tumor, they simultaneously treat drugs as signal-creating tools, enrich the drugs by specifying the drug-target relation, and advance the oncologists' understanding of cancer biopathology by exploring the mechanisms underlying treatment response. The informationally enriched anticancer agents thus become probes that can be deployed to explore mutations, pathways, and their shifting relations under pharmacological intervention. These relations between drug signals, mutations, and pathways thus turn into dynamic epistemic objects in their own right.

The alternating status of drugs as informed and informing materials provides the answer to a possible objection to our main argument, namely that insofar as drugs have emerging, context-dependent rather than fixed, intrinsic properties they cannot act as probes. In other words, lacking the stability that defines technical objects, they can hardly perform the independent informing task we ascribe to them. But it is exactly this temporary stabilization that results from informational enrichment that allows them to act as informing materials, *for the time being*. Rheinberger's (1997) discussion of experimental systems, which has been extended to clinical experimental systems (Nelson et al. 2014), mentions a similar alternation of epistemic things that become technical objects and *vice versa*. Even more relevant for our argument is his claim that "the variable intersections between instruments and objects … form the critical zone in any experimental system" (Rheinberger 2010, p. 218). This is particularly true of the new designs of genomic-driven clinical trials that, by turning them into clinical experiments,

reshape the organizational and epistemic relations between all participating entities (researchers, molecules, institutions, etc.) and allow temporarily stabilized experimental drugs to act as informing materials.

Driving the change

At this point, one might be tempted to ask whether the crucial development that drove all the other changes we examined in this paper can be ascribed to the arrival of cheaper and faster genomic sequencing technologies. Initially, targeted agents were not closely coupled with sequencing. For instance, treatment with trastuzumab, another early example of targeted therapies, is predicated upon testing for the overexpression of the HER2 gene. Such testing, in spite of concerns about its accuracy and inter-laboratory consistency, was routinely performed using more traditional pathological techniques such as immunohistochemistry or early molecular techniques such as Fluorescence in situ hybridization or FISH (Cambrosio et al. 2017). This kind of HER2 testing was mostly confined to pathological and clinical laboratories, and did not translate into full-fledged experimental investigations of tumor biopathology. In the case of the aforementioned EGFR receptor molecule, also one of the early targets of a new class of drugs, it took several years before clinical researchers felt a need to explore EGFR mutations and relate them to patients' differential response to targeted agents. As a leading clinical researcher retrospectively commented:

> If you had an EGFR kinase inhibitor and you said, "I'll give you one experiment that you can do – just one! – to think about where the vulnerable point might be," well, you would look at the EGFR kinase region, right? Because it's so obvious, and yet nobody did. So, it wasn't like it was some complicated signaling cascade that you had to figure out, or some epigenetic or transcriptomic mechanism; this was really, really obvious. And yet, nobody did it initially… I mean the idea is so simple and obvious – and I think now we realize it's obvious. (Interview with Dr. Razelle Kurzrock, August 2014)

We would argue that a key factor in creating this retrospective feeling of obviousness, in addition to developments in sequencing technologies, is the transformation in how drugs were problematized in the clinical research context. The impetus to use EGFR as a predictive biomarker to guide therapeutic protocols arose once clinical cancer researchers realized that the use of targeted drugs such as EGFR inhibitors would lead to insights into the biopathological mechanisms. Establishing the experimental importance of EGFR inhibitors (their role as informing materials) was a crucial step for confirming the value of the molecular characterization of patients' tumors in the informational enrichment of this class of agents. The EGFR case has in the meantime become a paradigmatic example of the implementation of sequencing approaches in association with the use of targeted drugs.

Additional insights into the crucial role that drugs play in reconfiguring the experimental and organizational structure of clinical research are provided by debates amongst oncologists about clinical trial designs. For reasons that cannot be discussed here (but see, e.g., Redig and Jänne 2015), traditional models of clinical trials have come under criticism for their inability to cope with the onslaught of new experimental substances and analytical techniques. Oncologists and biostatisticians have been busy designing alternative approaches, and a few landmark trials have been performed, such as the BATTLE trial (Kim et al. 2011) and Lung-MAP, a trial sponsored by the NCI (Herbst et al. 2015), both of which assess the activity of targeted agents in the presence of selected biomarkers. These 'biomarker-driven' trials, despite their novel designs, share with pre-genomic trials a common purpose of focusing on the approval of drugs for specific indications and categories of patients. As such, they have been criticized by clinical researchers who are interested in investigating the biopathological mechanisms of drug response, rather than evaluating biomarkers as elements of the regulatory toolkit for approving new anti-cancer agents (Mansfield 2014). As noted by one of the critics:

> So, this type of [exceptional responders] approach really leads to a type of clinical trial where we want to ask a very simple question: When you have a MEK1 mutation, how often do you respond to the MEK inhibitor? That's the only relevant question at this point. It's not: Can we candidate a biomarker? Can we develop a companion diagnostic? None of that is important until we have some sense of how often these patients respond to a particular inhibitor. (Solit 2014)

These 'trials to learn' (about cancer biology) show how drugs have moved from being the object of informational enrichment (and regulatory evaluation) in clinical trials, to one of the elements constituting the trial as an experimental system in its own right. Drugs now inhabit a relational space they share with molecular target panels, mutational landscapes, and biopathological phenomena.

Concluding remarks: What's in a target?

Personalized medicine, most oncologists would argue, is about 'matching' targeted agents and molecular targets. Indeed, "appropriately pair[ing] target and therapy" is a central axiom of the personalized medicine program (Redig and Jänne 2015). Yet, the use of targeted agents to explore pathways as in the cases described above shows that there is no simple 'key-and-lock' or linear causality linking targeting agent and target. The targets themselves are neither fixed nor moving but anchored, so to speak, in the understanding of the mechanism of action of the drug itself and its effects on patients. As knowledge of cancer mechanisms evolve, so do the targets, their actions in normal and pathologic physiology, and the background against which they stand as 'targets'. A tyrosine kinase receptor, for example, is not strictly speaking a target in the common-sense meaning of the word target. It is not a thing. It is a both a place and a function, a way-station in a pathway which is itself a cascade of functions and effects. There is no easy way to separate once and for all the drug, the target, and the mechanism in

oncology, and their interaction renders clinical research as a form of research that does not easily fit into a matrix of drugs and targets. A quote from a recent paper examining the biopathology involved in inhibiting EGFR to treat colorectal cancers neatly illustrates our contention:

> Pathways rather than single genes should be the focus of studies aimed at dissecting the molecular basis of targeted therapies... once the "culprit" pathway governing the oncogenic property of a cancer is identified, all the players involved in that pathway (and not only a specific gene) can become a suitable therapeutic target (Benvenuti et al. 2015, p. 2643).

Therefore, 'targets', which turn out to be pathways, imply more complex processes, that are being explored as part of the clinical trials of targeted therapies. These trials elicit elaborate experimental work to unravel pathways as a necessary condition for drug development (i.e., continued informational enrichment of anticancer drugs). It is in that sense that, together with sequencing, drugs have become crucial research instruments in the emerging cancer clinical-experimental system. The relational space of subpopulations, regimens and substances that has been in place since the rise of chemotherapy, the space that produced drugs as informed materials is now acting as a toolbox of informing materials for the production of cancer phylogenies, mutational landscapes, and other emerging experimental objects. Drugs have become instruments that produce experimental signals in their own right. The expansion of the measurements they allow and the qualities they reveal have turned them into informing materials. The relational entanglement of cancer and drugs has resulted in a more dynamic understanding of the extreme variability and mutability of cancer. The deployment of this 'deeper' epistemic space stands in contrast to what leading oncologists now perceive as 'reductionist' single-gene studies, and comes with calls to deploy comprehensive molecular characterizations of tumors and downstream bioinformatics analyses that are able "to account for the complex biologic environment and the functional implications of mutational profiles of a tumor" (Stenzinger et al. 2015). In turn, this experimental turn signals a progressive dissolution of the boundaries separating the clinic from the laboratory.

This account of the repurposing of contemporary anticancer drugs as research instruments has implications for the study of experimental practice and cultures. For students of genomic medicine and translational research, it suggests that we view genomics as an evolving set of experimental systems rather than a mass-produced technological infrastructure for medicine. A corollary of this claim is that clinical research in molecular oncology is an experimental undertaking seeking knowledge of disease mechanisms, and not simply a handmaiden of evidence-based medicine. Secondly, the dissolution of the concept of therapeutic target into sites and signs distributed along biopathological pathways further chips away at any clear boundary between the clinic and laboratory-based research. Our analysis shows that the advancement of mechanistic knowledge in the field of molecular oncology now partly

rests on clinical experiments that use cutting-edge and edge-defining drugs. As previously mentioned, clinical researchers who seek to understand the molecular pathways driving cancer development proactively contact pharmaceutical companies to elicit drugs inhibiting the pathways they are investigating. This (and other examples provided in this paper) clearly point to a realignment of the relations between clinical researchers, pharmaceutical companies, producers of (sequencing) instruments, diagnostic devices and software, and regulatory agencies, leading to the establishment of an increasingly seamless web of biomedical research and treatment.

There are three additional, broader reasons why our analysis of drugs as informing material has important implications for biomedical science and technology studies. Consider, first, the nature and role of clinical trials, the central component of clinical research. Often portrayed as the gold standard of evidence-based medicine, this view of clinical trials portrays the underlying therapeutic mechanisms as a somewhat reductive black-box whose purpose is to evaluate a simpler term: efficacy (Howick, 2011). And yet it is clear that clinical research encompasses a much wider scope of activities than simple drug and device testing. As detailed in this paper, nowhere is this more evident than in the domain of anticancer drug development. Philosophers and historians of medicine and biology, however, tend to elide the fecundity of clinical trials as an experimental resource. There are, of course, exceptions. For instance, Adam (2005) has found that the elucidation of biopathological mechanisms and the testing of agents are inseparable components of the development of drugs in cardiovascular diseases. But exceptions are not the rule, and we need to be more systematic in our exploration of how drugs and mechanisms are investigated and deployed in the clinic, which has today become a central site of knowledge production in the field of oncology.

As Nelson et al. (2014) have argued, and as this paper has further substantiated, oncology clinical trials, far from being mere testing devices, stand as full-fledged experiments. While this was arguably already the case during the second half of the 20th century (Keating and Cambrosio 2012), this fact has become increasingly apparent since the turn of the new century. Indeed, the transformation of drugs into informing material makes such a conclusion inescapable. This helps explain, for instance, why Contract Research Organizations—firms to which pharmaceutical companies turn in order to outsource the routine clinical testing of drugs (Mirowski and Van Horn 2005)—have made fewer inroads into a research-intensive domain such as oncology.

A second implication of our analysis is that drugs and diseases are coproduced, a point that acquires its clearest expression in the fragmentation of common diseases, such as breast cancer, into an increasing number of rare diseases, each defined by a specific combination of molecular biomarkers that simultaneously act as potential or actual targets (Keating et al. 2016). The molecular landscape of tumors can thus be explored through the deployment of targeted drugs. This ‘molecularization of diseases’ (Shostak 2010, Hogarth et al. 2012, Bell 2013), as we have seen, does not merely redefine disease phenotypes; rather, targeted drugs, as informing material, destabilize the very notion of

'targets', thus adding a looping dimension (Navon and Eyal 2016) to the molecularization process.

A final consequence of our analysis concerns the pharmaceutical industry and its role in the production of biomedical knowledge. Several authors, both from inside (e.g., Angell 2004) and outside (e.g., Courtney and Abraham 2013) the medical world, have fiercely criticized the pharmaceutical industry and the regulatory agencies in charge of overseeing it. For instance, commenting on new regulations introducing an accelerated approval path for cancer drugs, Courtney and Abraham (2011) claimed that this decision "should be regarded primarily as part of a deregulatory regime driven by the interests of the pharmaceutical industry in partnership with all major aspects of the state." Courtney (2015), referring to the trope of the 'pharmaceuticalization of society' (Abraham 2010, Williams et al. 2011), has denounced the "inappropriate and overly aggressive use of drugs" in the case of patients with "advanced, incurable cancer." Rather than highlighting the dismantling of regulations by neoliberal policies, and the nefarious influence of pharmaceutical companies, the present paper has focused on the evolving experimental strategies in the biomedical domain, on how they increasingly draw on clinical practices, and on the role of novel biomedical entities and platforms in this regard. And yet, this paper is also relevant for the aforementioned literature insofar as critics of the pharmaceutical industry have often entertained the idea, explicitly or implicitly, that it is somehow possible to separate the wheat from the chaff, i.e., to purify medical knowledge by purging the undue influence of commercial drug companies. In view, however, of the entanglement of drugs and research when drugs act as informing material, the situation now appears far more complex, as no bright lines can be drawn between contemporary biomedical knowledge and the tools used to generate that knowledge.[6] Drugs, in other words, and the companies producing them cannot be reduced to a mere epiphenomenon of contemporary biomedicine: they are an essential component of what and how we know.

[6] See Greene (2007) for a somewhat similar argument concerning the role of pharmaceutical marketing.

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FIGURE CAPTIONS

Figure 1: Summary view of chemotherapy mechanisms circa 1969. Source: Karnofsky (1968, p. 233). Reproduced with the kind permission of John Wiley and Sons.

Figure 2: Pathways and resistance mechanisms in renal cell carcinoma circa 2009. Notice that the drawing includes, in addition to the names of the molecular components of pathways, the names of drugs blocking specific molecules. Source: Rini and Atkins (2009, p. 993). Reproduced with the kind permission of Elsevier.