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Explanatory Puralism in Oncology: The Case of Neoantigen-Based Adoptive Cell Immunotherapies

Luca Chiapperino, Nils Graber and Francesco Panese

Introduction

Precision oncology is often associated with the emergence of genetic, and later genomic technologies across the 1990s and early 2000s. At the crossroad of technical, experimental, and theoretical developments in cancer research, genetic processes gradually became the main biological drivers of tumorigenesis. The accumulation of DNA mutations in healthy cells – thus goes a typical genomic claim about cancer origin (Plutynski 2018: ch. 3) – is the main biological process that turns 'normal' tissue into cancerous cells. The increasing availability of tools to dissect cancer mutational patterns has made genetic mutations relevant not only for an understanding of tumorigenesis. Rather, today cancer genetics/genomics constitutes a specific type of experimental care (Cambrosio et al. 2018) that aligns knowledge of tumour mutational landscape with specific treatment strategies. Understood as such, each cancer cell provides a set of genetic signatures or 'hallmarks' (Hanahan and Weinberg 2000, 2011) that both explain why cell circuitry goes into disorder, and constitute a molecular target for pharmacological intervention. Accordingly, the precision therapeutic program inspired by genetics builds upon the 'holistic clarity of mechanisms' (ibid., 2000: 67) explaining the functional characteristics of a given cancer, and leverages the use of specific drugs (so-called 'targeted therapies') to counter them (Hahn and Martin 2015).

Since the 2010s, however, precision oncology has become increasingly bound also to cancer immunology, and the corresponding therapeutic program of immunotherapies. Reviving long-standing evidence of the importance of the immune system in cancer,[1] immunology regained the central stage of oncological research when drugs targeting immune-checkpoint inhibitors were considered as a major clinical breakthrough in 2013. A bit later, in 2018, James Allison and Tasuku Honjo received a Nobel Prize for their discovery of immune-checkpoint inhibitors. The targeting of these inhibitors exemplifies well how different is immunologists' approach to tumorigenesis from that of

genomics. These drugs rather target the 'brakes' tumour cells put on the immune system (the surface proteins PD-1 and CTLA-4) to prevent the patient's immunological response against cancer. Therapies targeting immune-checkpoint inhibitors PD-1 or CTLA-4 thus aim at removing the barriers that stop immunological agents, such as T cells (CD8), frequently termed as 'killer cells', from detecting the tumour and eliminating it. Along the same lines of reasoning (and experimentation), the repertoire of cancer immunotherapies has recently expanded into several other immunological agents besides checkpoint inhibitors. Importantly, adoptive cell therapies (ACT) consist of expanded or engineered autologous Tumour Infiltrating Lymphocytes (TILS, i.e. T cells found in the patient's tumour) that get selected for their immune reactivity and expanded *ex vivo* for reinjection into the patient. Another example of immunotherapies are vaccinations through autologous dendritic cells, which are a specific sub-population of immune agents presenting tumour antigens to the adaptive immune system (Tanyi et al. 2018). Some of these therapies have already obtained regulatory clearance, such as CAR T therapies (i.e. a form of ACT relying on a genetically modified cellular receptor),[2] and more are underway for approval. According to the FDA, more than 2000 active cell therapies are in fact under development in the year 2021.[3]

Within the promissory landscape of 'precision oncology' (Rosenberg and Restifo 2015) immunotherapies are a distinct therapeutic program from genome-based targeted therapies. Focusing on the patient's own biological material and its therapeutic potential, precision immuno-oncology pursues a strategy that is not centred on a few biological hallmarks of tumours as targets of intervention. Rather, it operationalizes an explanation of cancer as a process involving tumour microenvironment, tissue organization, the host's immune system and cell's capabilities to escape its control. More than a few biological hallmarks of cell functioning, cancer gets addressed here as disrupted cellular and tissue-based homeostasis. This immunological view recasts genetic drivers as one among the many factors of tumorigenesis, and points to the multi-dimensionality of this phenomenon at the biological level (Rondeau et al. 2019).

But how do these contrasting biological explanations of cancer structure distinct forms of biomedical work? Are genetic and immunological representations of cancer an *alternative to, articulated with, or enabled by one another in precision oncology*? That is, how do 'the intricacy', the contrasts and the 'complementarity' (ibid., 5) of these two explanatory frameworks play out in practical settings of oncological research? To answer these questions, this chapter draws on interviews with researchers and clinician-researchers working in a platform for the development of ACT in Switzerland. Consisting of the *ex vivo* expansion and reinfusion of T cells from patients, this form of immunotherapy is currently being developed with the aid of tools for the selection of immune cells most specific to the mutational landscape of patient's tumour (i.e. its neoantigens). First, the chapter details how experts in this setting diverge on ideas, tools and heuristics to explain cancer. These positionings are akin or related to the opposition between the so-called 'somatic mutation/clonal' mechanistic theories of tumorigenesis and the holistic approaches like the 'immunological' views of cancer (Bertolaso 2011, 2016; Pradeu 2019). Second, the chapter details the pragmatic ways these epistemological points of view are brought together through a specific epistemic and organizational work which enables *a minima* the functioning of both material

configurations of shared research infrastructures and a common therapeutic program of precision immuno-oncology.

Before proceeding with our analysis, some terminological clarification is in order.[4] The theoretical propositions of our informants get also called 'theories' or 'conceptions' of cancer, such as in the case of the Somatic Mutation Theory, the Clonal Genetic Model, or the Tissue Organization Field Theory. We will refer to these theoretical propositions/models as 'explanations' instead of 'theories'. The reasons are multiple. First, because if these different viewpoints were full-fledged theories, they would be axiomatized and closed theoretical frameworks. Yet, neither genetic nor immunological 'models (and explanations) of cancer' impose such heavy formal constraints. Rather, they are both 'often partial and sometimes overlapping' (Plutynski 2018: 11). Second, we privilege talking about explanations because these theoretical views of cancer are 'work in progress' (Malaterre 2007: 68). Both of them cannot represent all known aspects of cancer biology and progression but can nonetheless provide an empirically and theoretically adequate answer to the question 'what is cancer and why does it arise?'. As shown in philosophical debates on scientific explanation (Woodward and Ross 2021) this is what typically distinguishes an explanatory query from a theory. Third, genetic or immunological perspectives on cancer are explanations also in the sense that their role is fundamentally pragmatic: they both play an important epistemic and social function within the scientific community. They constitute practical indications as to how to inquiry into the relevant mechanisms of cancer development and progression. They represent heuristic principles alternative to one another; namely, they translate into diverging working hypotheses, claims formulated at different biological levels, guidelines as to what processes to study and investigate to provide relevant discoveries for cancer research. Furthermore, their practical uptake is also allowing practitioners to position themselves in the community of cancer researchers. Being an immunologist, or a genomics expert can be an oppositional element as to ways of interpreting, apprehending and articulating experimentations on cancer.

Our study suggests that, while differences abound, the gap between these alternative explanations of cancer might be far narrower than postulated by those who consider them incommensurable theories of cancer (Soto and Sonnenschein 2011). Issues of integration and compatibility are seldom discussed by the concerned actors in daily collaboration, nor they prevent common experimentation. Theoretical debates rather get superseded by a pragmatic slant shaped by the material and organizational constraints of participating into translational research on precision immuno-oncology. This socio-epistemic process offers us the opportunity to conclude on the insights that social science methods provide to philosophical questions of incommensurability between theoretical presuppositions and explanations in cancer research.

Context of research, materials and methods

This chapter draws from an ongoing project documenting the socio-technical assemblage of a translational pipeline of precision immuno-oncology at a university hospital and its contiguous new cancer research centre (henceforth NCRC) in

Switzerland. Specifically, the research materials for this article stem from two rounds of interviews and observations with researchers and clinician-researchers at the NCRC. The first round (conducted between 2018 and 2019; Interviews N=20) focused on the organizational and epistemic process triggered by the architectural design and implementation of research activities at the NCRC (see Chiapperino, Graber and Panese 2021). The second round of fieldwork consisted of a dive into the main translational research pipeline at the NCRC. We conducted observation on the development in both laboratory and clinical research spaces of the practices associated to two types of autologous therapies currently under development. On the one hand, ACT consisting of either TILS or CAR-T cells, which are selected from tumour histological samples, expanded *in vitro* and in some cases genetically engineered *ex vivo* in a facility meeting Good Manufacturing Practices (GMP) standards. On the other hand, cancer vaccines produced through dendritic cells extracted from the tumours of the patients. Translational research projects on both families of treatments share several experimental steps: both ACT and vaccines integrate immunopeptidomics (i.e. a technique dissecting the protein complexes involved in cancer's eliciting of immune responses) with bioinformatics and Next-Generation Sequencing techniques analysing somatic genetic alterations of tumours (Huang 2014). In both cases, immune cells have to be screened, selected and expanded through *in vitro* and cell-based methods in order to identify the population of immune cells (e.g. T-cells, TILS, dendritic cells) with the highest specificity vis à vis the mutational landscape of patient's tumour. The interviews (conducted between 2019 and 2020; N=14) and observations around these practices explored the epistemic dimensions of developing these precision immunotherapies. Part of the questions addressed the actors' experimentations with the in-compatibilities between immunological and genomic concepts, practices and tools of cancer research. This round of fieldwork took place mostly during the COVID-19 (year 2020) pandemic and was performed with a combination of videoconferencing tools and classical qualitative methods. Our research project meets all local ethical requirements.

Competing biological explanations of cancer in the NCRC

The 'reductionist perspective' on cancer anchored on genes has dominated cancer research in the last 50 years', and is still central to the experimental program of 'precision oncology' (Bertolaso 2011: 516). Originally known as the Somatic Mutation Theory (SMT), this explanatory framework pivots on mutations – to be understood generally as a change in the DNA sequence of somatic cells – as explanantia of the biological specificities of cancerous cells vis à vis normal cells (ibid., 2016). Propelled by the discoveries of the first oncogenes across the 1970s and 80s, cancer research has rapidly come to be dominated by such theoretical/explanatory models of cancer. As SMT goes, mutations accumulate in a cell up to the point of hitting oncogenes which promote uncontrolled proliferation of the cells and transform normal tissue into tumours cells. This means that gene-related events (e.g. mutations, translocations, etc.) and their consequences on the internal mechanisms of the cell constitute, under SMT, the basic

building blocks of cancer biology (Hanahan and Weinberg 2000, 2011). A different, yet cognate version of this explanation emerged after the 1980s, when the received view on mutations got complexified by the characterization of tumour suppressor genes. Not only mutations at the basis of tumorigenesis imply the acquisition of tumour-specific functions of the cells, but these mutations also entail the loss of the tumour-protective functions normally present in cells. Known as the Clonal Genetic Model (CGM) of cancer, this amended version of SMT points to the heterogeneity of mutations in cancer cell populations, and to the selective overgrowth of monoclonal sub-populations of tumour cells (each with specific properties stemming from genetic mutations) as driver of disease progression (Bertolaso 2016; Plutynski 2018). Considering the explanatory relevance of mutations in SMT and CGM (henceforth SMT-CGM), it is not surprising that the associated style of practice of cancer research is one that reduces causation to a few single elements in the cell. Cancer emerges from a 'wired, embedded, cellular system' (Bertolaso 2011: 521) whose defining elements are cumulative mechanisms producing a complex biological phenomenon. It is then the study of the 'hallmarks' of cancer biology (Hanahan and Weinberg 2000, 2011) – namely, the functional capabilities tumors develop from genetic alterations – which become the central focus of oncological research under this 'mechanistic research program' (Plutynski 2018: ch. 3).

Dominant explanatory frameworks such as SMT-CGM certainly played a major role at a global scale in producing concrete configurations of cancer research. Their role can also be gleaned from the local configuration of the NCRC. It is in fact through the confrontation with SMT-CGM that the local research program of precision immuno-oncology comes to be interpreted, apprehended, and articulated conceptually. As expressed by several of our informants, 'the fact that cancer is triggered by some genetic aberration' is the default view, the one that is hardly disputed in scientific circles and that constitutes 'the very basics' of precision oncology (Bioinformatician). Yet, most of our respondents know that the answer to the questions 'what is cancer?' and 'why do cells turn into tumours?' might be 'very different' among researchers at the NCRC (Clinician-Immunologist). In the words of a PI with a track record of cancer genomics that dates to the pioneering characterization of oncogenes in the US:

> I would like to see the answers of my [immunology] colleagues! What I define as cancer is a genetic disease, so I don't know how much this is biased by my genomic approach [she laughs]. But, for me yes, cancer is a genetic disease. *Cancer is something you acquire through mutations*.
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> Molecular Biologist-Genomics Expert, our emphasis

While presented as the default explanation for cancer in the research community, SMT-CGM is not without controversy (Bertolaso 2016). On this point, the arguments of our respondents and those of philosophical and biomedical critics intersect consistently – although with different levels of formalization. As many point out, SMT-CGM is a poor explanation of tumorigenesis. Some researchers at the NCRC doubt that causal claims of cancer genetics and genomics are the most relevant explanatory propositions. 'When you look at those tissues', claims a Clinician-Immunologist, 'it's true chaos'. Many

things, he argues, 'happen at the same time in different areas of the tumor, at the genetic or epigenetic level, and so on'. Otherwise stated, the claim that mutations alone can explain this 'hugely complex' process is not believed to hold water. As formalized in the philosophy of science and medicine debate by Anya Plutynski's seminal work (Plutynski 2018), this kind of critiques to SMT-CGM do not deny that genes are causally relevant to cancer. In the words of another respondent, 'no one would argue with the idea that, you know, genetics is an important component of cancer development' (Translational Researcher-Biologist). But, things get controversial when at issue is the claim – bona fide attributable to SMT-CGM – that genes are the actual *difference makers* in tumorigenesis. The causal role of genes, critics reply, depends on the context. While, for instance, a mutation to the *p53* gene in a cell is certainly a causal factor for cancer, you 'cannot separate this cell from the rest of the body. What should have been developed and was eventually not developing, or viceversa, is always due to an interaction of different factors' (Immunopeptidomics Researcher). A strong focus on genes and their explanatory status ignores, in other words, the causal intricacies behind cancer (Bertolaso 2011; Rondeau et al. 2019). On the one hand, philosophical and biomedical critics point out that the causal factors for cancer intricately interact with one another: genes are unable to provide an embedded, unified, linear explanatory network to account for the biology of cancer. Both environmental factors and organismal complexity play a fundamental role and are incommensurable to genetic explanations. On the other hand, SMT-CGM ignores that cancer is a temporally dynamic and ever-changing process. Some biological processes might be crucial to gain tumour-specific functions (e.g. mutations), but then might fade away to give way to others (e.g. immunological sculpting, vascularization, etc.) as the tumour advances through stages of the disease.

Highlighting these limitations of the SMT-CGM model plays a specific role among our respondents. More than the debunking of a theoretical affirmation of SMT-CGM, it suggests abandoning the focus on genes as main heuristic assumption of cancer research (Malaterre 2007). Otherwise stated, it is a resolution directed at practices more than concepts, which encourages scientists to deviate from genes as main working hypotheses, experimental objects or targets of intervention of translational research. As a corollary, these critiques offer to NCRC researchers the possibility to claim the relevance of other research programs and connected explanations. Cancer development can no longer be assumed to be solely a matter of mutated genomes; hence the search for alternative explanations and causes. Chiefly, at the NCRC, this is the case of cancer immunology.

Several respondents elaborated on immunological research as a much needed shift from widespread explanatory assumptions about cancer. For instance, one PI insisted on the fact that mutations cannot account alone for cancer as clinically relevant manifestation of the body, and that immunological editing of tumour cells, which is today the target of immune checkpoint inhibitors treatment, is the missing bit of the puzzle for that matter:

> It is believed that, since mutations generate aberrant proteins, the immune system can recognise cancer cells very early. Many tumours are actually eliminated at an early stage. Key to this process is the immune system. But tumours are, we like to

> say, smart. So, they can escape and become invisible to the immune system. *But now we know that and with immunotherapies we can reinstate an immune response. This was not obvious before and this is why it is a revolution theoretically*.
>
> Biologist-Immunologist, our emphasis

While described as 'revolutionary' or 'paradigm-shifting' also in the literature (Finotello and Eduati 2018: 1), this evidence on the importance of the immune system in cancer has long co-existed along the knowledge of the genetic aetiologies of cancer in the twentieth century.[5] Yet, as this informant reminds us, the recognition that the tumour's immune environment is an ecosystem affecting tumorigenesis and tumour evolution suggests a radically different explanation of cancer from SMT-CGM. Two seminal articles by prominent immunologists Dunn and colleagues may be useful to illustrate the claims and evidence that support this view. They describe the multiple ways the immune system acts in relation to cancer through both 'host-protecting' and 'tumour-sculpting' actions (Dunn et al. 2002: 991). Briefly put, the immune system plays a pivotal role in tumour development through three distinct processes known as the 'Es' of cancer immunoediting (Dunn, Old and Schreiber 2004). First is the 'elimination' phase. This process, whose characterization as 'cancer immunosurveillance' has a far longer history than precision oncology (Old and Boyse 1964; Klein 1966), consists in the eradication of developing tumours through immune responses acting on distinctive structures of tumour cells – called 'antigens'. Second, the immune system operates also through a process of 'equilibrium'. This occurs only if the first step fails to eradicate the growing malignancy and consists of a careful attunement between immune components (such as lymphocytes) and the cellular variants of cancer that survived elimination. Equilibrium is a highly dynamic process which consists of the continuous sculpting of immune responses in the face of an iterative selection among cancer cells' antigens (due to their genomic instability) (Quezada et al. 2011). Finally, particularly resistant cancer cell variants selected in the equilibrium phase can also 'escape' immune responses. In this phase tumour development relies on both changes intrinsic to the tumour cells (e.g. mutated antigen expression that prevent immune recognition) and modifications hampering the host's immune response (e.g. the tumour's secretion of signalling proteins, like cytokines, with immunosuppressive effects) (Marincola et al. 1999; Khong and Restifo 2002). Escaping immune detection means also that tumours can expand often reaching a metastatic state.

Advances in the understanding of these three key processes have greatly increased the place of immunotherapies in the 'epistemic space' (Müller-Wille and Rheinberger 2007) of contemporary oncology. Primarily, as we mentioned in the introduction, the field has witnessed the development of immune checkpoint inhibitors, which act precisely on the 'brakes' the tumour puts onto the immune response of the patient (Mellman, Coukos and Dranoff 2011). Yet, also ACT and other types of immunotherapies have followed the path of checkpoint inhibitors by leveraging immunoediting thinking and producing landmark findings of patient remission in need of further validation (Jiang et al. 2019). However, of relevance here is that immunoediting exemplifies the main tenets of immunological explanations of cancer, and how they differ substantively from SMT-CGM (Pradeu 2019). As resumed effectively by one of our respondents:

> Of course, people define cancer differently: it is in part an unknown scientific matter, but also it goes into philosophical reflections. We know that cancer arises from a cell that goes bizarre, but why it does so, we don't really know. There are likely multiple decisive molecular alterations: genomic, epigenetic alterations. Of great importance is that the immune system can no longer keep the homeostasis of the tissue. So, actually, a lot of tumour biology is tissue immunology: non-immune cells and the immune system make together a balanced system which can become disbalanced. *Cancer is the broken state of such homeostatic balance: this can be a in a single cell, so clonal, or it can simultaneously happen in several cells. It is an extreme combination of different factors and a cumulation of bad luck.*
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> Clinician-Immunologist, our emphasis

Here, again, our respondents' claims cluster around a specific set of analyses of the epistemological foundations of cancer research. These explanatory claims differ primarily from SMT-CGM because multiple causes at various levels of biological organization produce cancer. They are cognate to a declaredly organicist framework known as the 'tissue organization field theory' (henceforth immuno-TOFT) (Soto and Sonnenschein 2005, 2011). From the disruption of tissue architecture, to shifts in the microenvironment and the immune surveillance of the tumour, this interviewee's answer frames cancer as a disease of 'multicellularity and, more specifically, of the cohesion of the multicellular organism' (Pradeu 2019: 43). General tumorigenic events under this (and similar iterations of) immuno-TOFT consist of the perturbation of the local tissue of concern. In the plainer terms of a translational researcher at the NCRC, those explanations of cancer similar to immuno-TOFT see it 'as a disease coming from our own tissues, which become totally dysregulated and start growing uncontrollably'. This micro-environment then elicits a response of the immune system, which attempts to repair or maintain the tissue, in ways that favour a clonal selection of tumour variants with decreasing immunogenicity. Cancer is, in other words, 'a corrupt manifestation of the physiology of tissue biology' (Biologist-Immunologist); the processes regulating it are 'basically those immunological processes a tissue and an organ consist of' (Clinician-Immunologist). These answers suggest that, under immuno-TOFT cancer is rather a diachronic and complex process and not a phenomenon reducible to genetic processes (Bertolaso 2011). It happens at the tissue's level of organization and through interactions that involve the whole organism, physiological processes gone awry, and the homeostatic balance produced by the immune system (Sonnenschein and Soto 2016).

Furthermore, researchers at the NCRC touch upon another major point of divergence between immuno-TOFT and SMT-CGM: the role of DNA mutations in cancer development and progression. Some agree with proponents of TOFT that these are not the drivers of tumorigenesis. Rather, mutations are 'hits' (Translational Researcher-Immunologist), epiphenomena of higher-level disruptions of tissue organization (Rondeau et al. 2019). Far from being the sole initiators of neoplastic expansion, progression and dissemination, mutations are rather part of a complex dynamic of causation with other components of the tissue: the cell, its microenvironment and the

immune system all partake to this process. Cancer arises from things 'happening at the same time in different areas of the tumor, at the genetic or epigenetic level', as a clinician immunologist reminded us above.

These declared iterations of immuno-TOFT co-exist however with less clear oppositions to the centrality of genetic mutations for explanations of cancer. When asked 'what is cancer', a researcher with a strong translational orientation primarily insists on one of the fundamental propositions of the mechanistic program of SMT-CGM, only to then complement it with the organicist perspective of immuno-TOFT. Cancer is 'a genetic disease, you know . . . or actually multifactor, there are different contributions. . .what is interesting and challenging is that the more years go by, the more we are realizing lots of different factors matter' (Translational Researcher-Biologist). Researchers at the NCRC do not always position themselves clearly vis à vis theoretical debates in oncology. They rather seem to 'incorporate claims from both theoretical approaches' or, as we shall see, 'to build bridges' across SMT-CGM and immuno-TOFT (Malaterre 2007: 69).

Working amidst a plurality of explanations

Contrary to the latest answer we examined, it may be too simplistic to see the convergence of SMT-CGM and immuno-TOFT as a sign of recent trends in cancer research. Historically, immunological explanations of cancer rather predate SMT-CGM itself. As one senior informant reminds us, also 'when [he] was a PhD student' oncology conferences featured a 'session on immunotherapies'. Yet, they took place in 'a very small room, large maybe like [an] office', because – he sentences – 'nobody cared' (Biologist-Immunologist). Hyperboles aside, theoretical, 'intellectual' interest for non-gene-centric approaches to cancer uphold by immunologists was never lacking, as another informant claims (Clinician Researcher-Immunologist). In this interview, the respondent reminisces about giving a seminar to his clinician colleagues about his PhD on the molecular mechanisms for the recognition of tumour cells by lymphocytes: 'Oncology people back then simply said "cool, good job, but it's just a pity it's immunology!"'. In the words of another respondent with a strong genomics background, it is undeniable that 'there was great research in immunology for a long time'; even if the fact that 'onco-immunology was there probably before targeted therapy' did not correspond to concrete ways of 'turn[ing] this [knowledge] against cancer' (Molecular Biologist-Genomics Expert). The limited clinical success of past immunotherapies gets narrated as the factor that drew the oncology field away from the explanatory relevance of cancer immunology. But the decisive results brought about by immune checkpoint inhibitors across the 2010s contributed to turn this situation around, and to re-activate conceptually (and experimentally) these ideas in a further new 'wave of enthusiasm' around onco-immunology (Löwry 1994, 1996). The question remains as to how and why heuristic presuppositions such as SMT-CGM and immuno-TOFT are brought together today in the specific experimental, institutional, and organzational setting of the NCRC.

Do SMT-CGM and immuno-TOFT share an explanans?

Some actors deem explanatory frameworks such as SMT-CGM and immuno-TOFT compatible through the designation of a *common explanans* like DNA. According to these interviewees, disagreements on the 'primacy of a few mechanisms' could persist, and people might quarrel over whether 'immune escape is key or not' compared to certain mutations (Bioinformatician). In other words, some propositions and formulations may differ across SMT-CGM and immuno-TOFT explanatory frameworks. Yet, there is little doubt that DNA and the genetic material are the molecular entities that explain both clonal and immunological drivers of cancer. Seeing DNA as shared explanans echoes those analysts that consider SMT-CGM and immuno-TOFT may 'just converge or collide' (Marcum 2009: 275) into a common explanatory framework. If we wanted to paraphrase the respondent above, the two explanations 'actually integrate neatly' because every cancer-related process can be reduced to the explanatory elements of genetic phenomena. In his words, cancer is necessarily molecular, and genetics is 'the molecular tool of life to store and use any type of information' (Bioinformatician).

Yet, even those who consider the claims of SMT-CGM and immuno-TOFT to be compatible on molecular grounds would underline that the 'amalgamation of these two approaches' is yet to be done (Marcum 2009: 279). As recognized also by other respondents, the disagreement is less on the recognition that DNA-based processes are relevant to cancer, than on the capacity of these biological processes to explain cancer causation under the two approaches – conceptually and in experimentation. SMT-CGM and immuno-TOFT, others would therefore argue, cannot converge (at least for the moment) on the explanans of DNA (Baker 2014; Bedessem and Ruphy 2015; Rosenfeld 2013). These frameworks even diverge on where to look for an explanation of tumorigenesis in DNA: while proponents of SMT-CGM insist on the centrality of studying mutations as read-out of tumour capabilities, immuno-TOFT proponents point to the recent evidence which shows 99.9% of tumour mutations to have little or no role in its development (Baker 2014). During an interview, we are told that if one's objective is to explain how cancer emerges through immunological escape, then mutations do not have to be studied per se, but only for their immunological effect. The rest of them 'are mostly false positives', told us an immunopeptidomics researcher. With a different presupposition in mind, akin to SMT-CGM, one would look at the mutanome (i.e. the ensemble of mutations in the genome) of cancer cells differently. Functions and capabilities of cancer cells are a direct emanation of DNA mutations and their systemic accumulation. Thus, the consequent experimental objective is rather investigating cancer progression as a unidirectional process of DNA and cellular decay. The shift in the genomic circuitry produced by mutations – and not only its immunological uptake – is here the relevant biological process explaining cancer (Rosenfeld 2013).

Another set of our respondents pointed instead to the need of performing a complex type of theoretical and practical work unifying coherently these explanatory stances (Bertolaso and Sterpetti 2019). To these interviewees, there is no existing explanans onto which the two explanations meet. If anything, these two explanatory frameworks are paradigms that have at best lost cogency and support in ways that suggest a

substantial 'instability' for both (Baker 2014: 1150). According to this view, what is needed is the development of a third-way, a 'multilevel explanation' that is not simply a synthesis of the two.[6] In the imaginative words of one of our respondents, researchers 'should introduce something like 'tumour immunity genes", meaning new conceptual and experimental entities that are capable of explaining how the 'extra layer' of the immune system works through 'basic mechanisms' of DNA functioning (Clinician-Immunologist).

Producing a practical convergence through experimentation?

One should underline that declaring the urgency of integration is not a hindrance for the activities of the NCRC. Theoretical disagreements do not impinge upon the pragmatic pursuit of a shared experimental program across researchers adhering to SMT-CGM or immuno-TOFT. Issues of explanatory convergence in the NCRC should be analysed also in light of a *specific experimental program* that makes immunological processes in cancer co-exist with the centrality of changes in the genetic components of the cell. Both those who consider theoretical integration feasible and those who do not are in fact involved in activities that mix tools, ideas and ways of knowing cancer of these two approaches. Research around neoantigens in the NCRC epitomizes this point.

Neoantigens are mutated proteins cancer cells present on their surface for immune escape. Specifically, they derive from the somatic mutations accumulated by the cancer cells and that selectively sculpt tumour immunity and immune response of the patient (Schumacher and Schreiber 2015). While antigens presented by tumour cells are an object of research since the 1990s (Liu 2016), it is through the 2010s that the link between genetic alterations of tumour cells and uniquely altered oncoproteins (neo-epitopes, or neoantigens) gets established (Jiang et al. 2019). As argued by a clinician-researcher with a long-standing experience in immuno-oncology research:

> I think that back then we worked on antigens that were very well known and characterized . . . we didn't know about the neoantigens, or maybe we knew about them, but, let's say, we did not think these would be the dominant ones. *The opportunity offered by the genomic tools available today is one of unprecedented analytical capacity. We might be able to completely redefine the clonality of tumours*.
>
> Clinician Researcher-Immunologist, our emphasis

As epistemic object (Rheinberger 1997b; Knorr-Cetina 1999) of oncological research neoantigens illustrate well how a research agenda shared by SMT-CGM and immuno-TOFT gets pursued in the NCRC. Primarily, this is enabled by experimentations at the crossroad of the epistemic and technical repertoires of these two views. On the one hand, the informant above makes clear that the availability of genomic tools is a major technical enabler of this process. Contemporary oncological research heavily relies on genomics as clinical/experimental system allowing clinicians and bench scientists to describe the heterogeneity of patient tumours. Biological characteristics of individual tumours such as their genetic mutations are relatively ordinary technical objects of

cancer research and experimental care (Nelson, Keating and Cambrosio 2013; Nelson et al. 2014). And the same goes for the biochemical assays that can investigate the composition of protein products, such as Mass Spectrometry (MS) techniques. In the words of another respondent, these technologies filled a 'technical gap' when applied to the study of immunological processes: they gave access to a whole level of understanding of the biology of cancer that was 'unheard of' in immunological circles (Translational Researcher PI-Immunologist). Genome sequencing technologies combined to bioinformatics methods are currently at the centre of much promise to produce reliable, scalable and standardized tools for precision immuno-oncology. Specifically, leveraging sequencing offers the opportunity to predict the unfolding of a crucial process in cancer immunology: how immunogenic proteins, such as (neo)antigens, get modified by the inherent instability of the tumour's protein-coding genome (exome). Similarly, MS-based technologies known as immunopeptidomics take the same biological process at issue but start from a molecular analysis of the proteins composing the antigens of cancer cells. High-throughput immunopeptidomics offers scientists a comprehensive overview of the proteins producing the immunocompatibility of cancer cells, and thus purports to identify those (neo)antigens with higher therapeutic leverage for immune agents. Needless to say, neoantigens are still unstable epistemic objects in precision immuno-oncology: sequencing or immunopeptidomics techniques have to be fine-tuned to specific circumstances to say something meaningful about neoantigens. The validity of neoantigen predictions is in fact often contested, in lack of reference standards and requires combination with traditional validation methods of higher reliability. Yet, neoantigens show that a materially-defined entity currently enables actors to black-box issues of hybridity, convergence and integration of explanations such as SMT-CGM and immuno-TOFT. These epistemological questions are not a hindrance to scientific activity in the face of an experimental object productively enabling collaboration in the NCRC.

On the other hand, the excerpt above also suggests that neoantigens are a fertile notion not simply because they leverage both the technical possibilities offered by genomics and those in the service of immunological views of cancer. Rather, they are narrated as potentially producing the compatibility between SMT-CGM and immuno-TOFT. As to immunological explanations of cancer: neoantigens are reported as the 'dominant' drivers of cancer escape and/or resistance from the immune system. Yet, they can theoretically also contribute to SMT-CGM: they derive from the DNA mutations defining cancer cells, hence they could help 'redefine the clonality of tumours'. More precisely, they add a clear dimension of genetic clonality and mechanistic functioning to the knowledge of antigen vs T-cell editing of cancer in immuno-oncology. In other words, neoantigens are both method and concept: they are a prolific way to put to work the tools of genomics much like they are a decisive mechanism (and promising explanans) to shape a systemic explanation of cancer biology. As such, neoantigens are at the core of a process of mutual shaping of the two distinct theoretical paradigms we analysed here. From a technoscientific point of view, they allow researchers to combine distinct experimental settings that fit the ideas, tools and ways of knowing of cancer of distinct explanatory stances. As epistemic object pursued through experimental systems (Rheinberger 2011), neoantigens play instead

the role of setting the stage the convergence of SMT-CGM and immuno-TOFT. They are a concept-object capable of providing an operational explanation of cancer that holds together principles of organic interactions among cells, organs and immune agents with changes in the elementary units of a cell like DNA.

Housing multiple explanations under the same roof?

One last aspect of the question regarding the co-existence of SMT-CGM and immuno-TOFT in the NCRC concerns the concrete efforts and opportunities scientists are given to debate and produce their integration. What is the place of these questions in the organizational setting and daily life of the NCRC? Are there dedicated time and space slots for producing an integrated explanation of cancer?

As we mentioned above, the NCRC pursues an integrative vision of translational science, which aims at producing precision immunotherapies, such as ACTs consisting of either TILS or CAR-T cells. The integrative objectives of the NCRC are explicit in the planning and organization of its architectural spaces (Chiapperino, Graber and Panese 2021). The architectural features of the building are planned and implemented to act as performative aligners of different approaches to cancer research. Far from being only a symbolic exercise, this architectural and organizational linkage is a technoscientific, material, organizational and regulatory activity (Stephens, Atkinson and Glasner 2008; Kaji-O'Grady et al. 2019). This includes planning the building's spaces, recruiting scientific actors who are likely to integrate, setting up spaces and activities that can transform territories of scientific activity and bridge approaches. The NCRC is designed in pursuit of such an epistemic ideal of collaborative research: pre-existing territories of cancer research get opened by displacement into a new common epistemic space (i.e. the NCRC) where social interactions and scientific activities are modularized, distributed and integrated in a common pipeline for neoantigen-based ACT development. At least in the declared intentions of its designers and managers, the NCRC's architecture is thus conceived as a major enabler of epistemic integration and hybridization. Specific to the question of scientific reflection and theorization, formal and informal 'bumping spaces' of the building are supposed to impact the sociality of scientific activity, and consequently collaborations and knowledge-production around common ideas. Ibid.

As the Conception Architect of the NCRC reminds us, the 'communicative qualities of the building' are however only 'an opportunity' for integration between complementary expertise and approaches. The realization of such an integration rather requires far more conditions to align besides architecture. Some interviewees doubt, for instance, that the professional environment of the NCRC can successfully enable the convergence of SMT-CGM and immuno-TOFT because of the selected recruit of researchers. Skewed in favour of 'people too close to immunology', the project risks betraying its original idea 'to bring the cancer community together'. As this interviewee rhetorically asks: are we sure that 'other aspects' of cancer will be investigated in a context with such a 'strong immunology background' (Molecular Biologist-Genomics Expert)? Another researcher points instead to the different distortions of the original project, which have taken place during the implementation of the building's plans in construction. The 'chill-out area' at

the end of the lab bays, she says, got emptied of the couches to make room for offices in the future; the 'discussion boots' have been moved 'in front of the offices' of senior researchers and scientific directors. The paradox, she concludes, might be ending up with a building that is designed to favour communication and exchange but has 'no space for creativity' (Technician-Immunologist): who would dare to spend part of her lab time to philosophize about cancer in front of the director's office? Finally, there is the room given to such type of work in the typical schedule of the NCRC researcher. Little or no time seems to be dedicated to exchanges on theoretical questions in the routine activities of most researchers. As one staff scientist reminds us on multiple occasions, this is probably 'a matter for PIs or research directors'. As she confesses laconically, 'discussion with fellow researchers has to stay more here [gesturing towards the floor] than at a philosophical level' (Translational Researcher-Immunologist). Time, efforts and resources for most staffers ought to prioritize the technical, experimental and clinical work of translational research: that is, the fine-tuning of analyses of each patient's tumour genome with an assessment of tumour immunogenicity, as in the case of neoantigen-based cellular therapies. Otherwise stated, there exists a clear hierarchy of cognitive work in the NCRC, which relegates the intellectual task of probing the potential convergence of SMT-CGM and immuno-TOFT to higher-level positions, while modularizing and distributing the experimental work across the rest of the staffers.

One could wonder whether this distribution of scientific work runs the risk of alienating the researchers at the NCRC. As illustrated by the last interviewee cited, the task of developing a unified approach is certainly a matter of concern across academic ranks – and also a source of frustration for those who are at the bottom of this hierarchy. Yet, the prolific experimental activities around neoantigens described above produce yet another, final modality of relating to the in-compatibilities between SMT-CGM and immuno-TOFT among our informants. A final set of researchers does not in fact contemplate, or even postulate the possibility of a coherent integration of these explanatory frameworks. A PI highly involved in this translational research and in clinical experimentation around ACTs describes entering a theoretical debate as something he simply may not be able, or willing to afford from his own position. His objectives are rather different:

> You may get scared with my answer. I started in 2013 in oncology at the department for therapeutic innovations: almost every day I realise that I should read basic textbooks about tumorigenesis. And, I still haven't done that. So, I live on a daily basis, in the department of experimental oncology, as an ignorant. *Yet, I think it would be utopistic to think – and that's the only example I have – that I could do what I do, working 14 to 16 hours per day, and pretend to have a decent understanding at such a higher level*. To be efficient in what I do, I need to focus on my very narrow little translational niche.
>
> Translational Researcher PI-Immunologist, our emphasis

The researchers working on neoantigens we encountered above took the pragmatic opportunities offered by this research as a driver of the convergence of SMT-CGM and immuno-TOFT. Without being capable to fully articulate or anticipate this

theoretical work, they postulated that a common experimental program around neoantigens may – sooner or later – provide a decisive mechanism (that is, a promising explanans) to shape a systemic explanation of cancer biology. This researcher emphasizes a different practical engagement with these matters through neoantigens. When pursuing the translational objective of developing novel therapies the epistemic objective of figuring out articulations across distinct explanations of cancer can be practically ignored. The therapeutic project of precision immuno-oncology at the NCRC – grounded on neoantigen-based ACTs – is therefore an activity that can be disjoined from a larger reconsideration of the theoretical foundations of this work. While the work around neoantigens of this translational researcher lies at the core of the converging trajectories of immunological and genomic concepts, the ensuing experimental practices do not need to grapple with the uncertainties and disagreements across these explanatory frameworks. Contrary to what one could expect, views about cancer do not need to go against one another, insofar as the objective is a relatively well-defined epistemic space (i.e. 'the niche' of neoantigen-based therapies).

Organizational, institutional and professional configurations of science can play a decisive role in keeping any effort towards the theoretical integration of SMT-CGM and immuno-TOFT in the background. While experimentations and architectures, epistemic, organizational and institutional activities, socialities and collaborations of science all play with the hybridities among distinct approaches to cancer, theoretical debates can still remain an unfinished, unaccessible, unaffordable, if not unnecessary matter for most NCRC researchers. These questions, we have shown, can be disjoined from experimentation and distributed across an organizational hierarchy of work that trumps individual preoccupations with theory-formulation. A pragmatic exigency impends on scientists to advance the NCRC's flagship translational research on ACT for the development of so-called 'precision' treatments in oncology. This quest for new therapeutic approaches can accommodate an agnostic plurality of explanations of cancer both as experimental and as organizational configuration.

Conclusions

In exploring questions of in-compatibility and convergence between SMT-CGM and immuno-TOFT within the NCRC we circled away from claims of incommensurability among these explanatory frameworks (Soto and Sonnenschein 2011). Even informants who think that concepts and evidence clustering around the two differ substantively do not consider these theoretical positions as fundamentally irreconcilable. Our interviewees' responses rather pointed to a pluralistic solution to these theoretical disagreements. While the explanations scientists provide certainly diverge – and they themselves are aware of this divergence – the fact researchers hold different views is interpreted as shaping a heterogeneous landscape of experimental orientations, and as a reminder that one challenge of their research is bridging the gap among theoretical and experimental traditions in oncology. In a nutshell, theoretical disagreements are acknowledged and relevant, but this does not suffice to regard SMT-CGM and immuno-TOFT as incommensurable paradigms (Marcum 2005, 2009; Malaterre

2007; Bedessem and Ruphy 2015). Quite the contrary, many go as far as arguing that these disagreements can and will be easily settled. The excerpts above have illustrated three versions of this potential integration. First, some see SMT-CGM and immuno-TOFT as already integrated because any biological process for cancer is fundamentally reducible to the explanans of DNA. Others consider instead this integration as work to be done: it is a task for the future and, of note, one that research on neoantigens may actually bring about. Finally, working with tools and epistemic objects such as neoantigens allows scientists at the NCRC to either black-box issues of convergence and integration (postulating them as a result that is yet to obtain from experimentation), or skip this question altogether by giving way to a strictly translational research agenda.

Let us briefly come back to the question we asked at the beginning: are SMT-CGM and immuno-TOFT *alternative to, articulated with, or enabled by one another in the setting of the NCRC*? Considering these different engagements with questions of incompatibility and convergence between SMT-CGM and immuno-TOFT, we contend that the answer to this question is: all of the above. First, these two frameworks exhibit substantive differences which pertain to many of the dimensions of what counts as 'scientific explanation' (Woodward and Ross 2021). SMT-CGM and immuno-TOFT are alternative to one another *qua* cell-centric and systemic *representations* of tumorigenesis, or as linear and multidimensional models of causality (Rondeau et al. 2019). These disagreements play out also around the *facts and entities* responsible for tumour initiation and progression. Divergences around the evidentiary role of DNA-related events (e.g. mutations, translocations, etc.), much like the role assigned to tumour microenvironment and the immune system neatly exemplify the difficulty to pinpoint common explanans across the competing claims of these views. Finally, the arguments, materials, assays, technologies and the claims stemming alternatively from SMT-CGM or immuno-TOFT do not speak in the same way within the *context* of different traditions of cancer research. Some of the actors we followed certainly support the view that it is a difficult task to resolve these explanations into one another.

Yet, the researchers at the NCRC also substantively articulate SMT-CGM and immuno-TOFT into a pluralistic research program of precision oncology. This finding of our inquiry rather supports the view that, though substantive at an epistemological level, the differences between SMT-CGM and immuno-TOFT are not metaphysical or irresolvable. As many have argued (Malaterre 2007; Marcum 2005, 2009; Bedessem and Ruphy 2015), while contrasts between these two explanations of cancer abound, we are likely *not* witnessing a case of Kuhnian incommensurability. These two theoretical representations and heuristic orientations of cancer research are rather structured models, experimental approaches and evidentiary claims that simply do not speak the same way to the whole community of practitioners. As explanatory disagreement (rather than paradigm incommensurability) this controversy does not require practitioners to adhere to one or the other to work together. There is an intrinsic heterogeneity and looseness to SMT-CGM and immuno-TOFT, as well as a series of contextual (organizational and technoscientific) factors, which allow scientists to adopt a pluralistic position on unresolved epistemological differences. On the one hand, supporters of both views adopt a multitude of strategies to articulate the two perspectives. They call for the importance of future theory-formulating, and/or they

allege the discovery of new entities (e.g. tumour immunity genes) that could resolve the differences between SMT-CGM and immuno-TOFT. Alternatively, they recognize promising aspects of the other explanation and produce complementarity by presenting them as different facets of cancer's biological complexity (Rosenfeld 2013). If the claims of NCRC researchers offer an illustrative overview of this theoretical dispute in contemporary precision oncology (and nothing suggests otherwise), they support therefore a specific argument about the alleged paradigm instability of SMT-CGM and immuno-TOFT (ibid.; Bertolaso and Sterpetti 2019). Since these explanatory frameworks are precisely 'not static and fixed but dynamic and malleable' presuppositions of cancer research (Marcum 2005: 38), their co-existence and articulation is the main preoccupation of scientists more than the prevailing of one over the other. As cancer is a complex and multifaceted phenomenon, scientists welcome a correspondingly complex and multifaceted epistemic culture of research. Claims in favour of the plausibility of each explanation can be cogently formulated starting from the available evidence in cancer research; and yet, no interest exists in the empirical or theoretical demonstration of the incompatibility or superiority between the two views. On the other hand, we have also highlighted the role of organizational, institutional – as well as architectural – arrangements of the NCRC in promoting a pluralistic scientific culture of precision oncology research. The project of the NCRC provides declaredly a common space for distinct expert communities in cancer research to thrive. Ibid. Communication is a visible and tangible element of its work environment. Yet, the purpose of staging, or at least promoting this reflexivity is less to position this research community on conceptual questions than to fit distinct experimental systems into a translational platform for patient-tailored immunotherapies.

Finally, these elements of practical import hint at the ways SMT-CGM and immuno-TOFT also enable one another in the NCRC. Taking the route of experimental practices around neoantigen-based ACTs we argued that the ideas, tools and ways of knowledge-making of genomics and immunology can actually converge into a shared translational research program. Of note, this research in the NCRC focuses on experimental junctures for translational research and leaves open the option that scientists remain agnostic on conceptual hybridities and in-compatibilities between SMT-CGM and immuno-TOFT. Research around neoantigens combines flagship experimental systems of one approach (i.e. sequencing of the protein-coding genome and mass spectrometry) with the characterization of a defining biological function of the other (i.e. mutated antigen presentation by tumour cells and their role in cancer immunoediting). While at a basic level this configures a complex experimental system where different traditions of cancer research converge, at another this configuration pushes the relevance of choosing between SMT-CGM and immuno-TOFT in the background. As we argued above, neoantigens are a fertile epistemic object which at best promises to drive a future full-fledged theoretical convergence, if it does not admittedly guard translational experimentations against these questions. For good or ill, the development and validation of a pipeline for ACT therapies and therapeutic vaccines production is the priority to pursue daily, even if this means neglecting the implications of such work on the validity and integration of distinct explanations of cancer. Neoantigens are, in other words, the enablers of a productive mutualization of

epistemic tools and play an important role in redirecting the focus of NCRC researchers away from the theoretical work needed to fully integrate SMT-CGM and immuno-TOFT. They are yet another 'boundary object' of the recent history of immunology,[7] which is both plastic enough to adapt to different theoretical conception of cancer, and robust enough to make the intersection of different approaches in oncology prolific.

Philosophical, or at least foundational issues such as formulating a comprehensive explanation of cancer are far from a clear solution. While some theoretical proposals for an overarching framework exist (Rosenfeld 2013; Bertolaso and Sterpetti 2019; Luo and Liu 2019; Rondeau et al. 2019), several problems persist when the coherence, in-compatibility and integration of SMT-CGM and immuno-TOFT are discussed (Bertolaso 2016; Plutynski 2018; Pradeu 2019). In this chapter, we have addressed this question through an approach some call philosophy of science-in-practice (Ankeny et al. 2011; Boumans and Leonelli 2013). Inspired by the questions, approaches and analyses of social studies of science and technology, this thread in current philosophy of science wishes to explore the theoretical, methodological and contextual processes through which scientists produce their theories and results. The typical questions of this research approach retain a strong epistemological character; thus, for instance, the question we explored deals with the foundations for in-compatibilities claims between SMT-CGM and immuno-TOFT on the side of cancer researchers. The methods chosen to answer this type of questions in philosophy of science-in-practice expand on the conceptual analyses typical of philosophy of science, to include social sciences and/or historical methods. Based on qualitative research materials, we have documented how scientists engage with questions of integration and in-compatibility of explanations in the scientific practices of a cancer research setting (i.e. the NCRC). While it is undeniable that SMT-CGM and immuno-TOFT still retain a great deal of practical, experimental and conceptual differences, our findings lean towards dismissing claims of incommensurability and raise the question of whether having a unified explanation of cancer is in any way necessary. The coherence of cancer research at the NCRC does not need theory-formulation to develop a conspicuous amount of synchrony and coordination. To paraphrase historian and philosopher of science Hans-Jörg Rheinberger in relation to the 'gene' in twentieth-century molecular biology (1997a: S253), our findings suggest precision immuno-oncology could acquire a dimension of integrated approach not as 'the result of alternative, organismic or holistic approaches called up to counteract reductionistic genetics and molecular biology'. Rather, 'local experimental sophistication' may provide a 'coarse' and yet prolific integration of *prima facie* incompatible claims on cancer. This is the lesson we wish to draw from our analysis of these philosophical and scientific problems as they unfold in the complex socio-epistemic gamut of cancer research.

Notes

1 As Löwy (1994, 1996) and Pradeu (2019) extensively argued, cancer immunotherapies developed through 'waves of enthusiasm' followed by periods of marginalization throughout the twentieth century. From Löwy's perspective, immunotherapies are a

boundary objects that links distinct research programs in oncology without necessarily constituting stabilized knowledge or a lasting approach to clinical practices. As Pradeu has shown, taking seriously the long-marginalized philosophy of cancer immunology means putting into question the theoretical, experimental and translational research programs currently dominating oncology.

2 'FDA Approval Timeline of Active Immunotherapies', n.d., available online: https://www.cancerresearch.org/scientists/immuno-oncology-landscape/fda-approval-timeline-of-active-immunotherapies (accessed 5 July 2021).

3 'FDA Cancer Cell Therapy Landscape', n.d., available online: https://www.cancerresearch.org/scientists/immuno-oncology-landscape/cancer-cell-therapy-landscape (accessed 5 July 2021).

4 We thank the anonymous reviewer who suggested this necessary clarification in our text.

5 We will not delve here into the historical and epistemological trajectories that have shaped the territorialization of oncology between immunological thinking and the dominant clonal paradigm of cancer. For an epistemological analysis of the place of immunoediting in corroborating SMT-CGM, see Germain (2012). For a socio-historical perspective on the field of immunology in the twentieth century cancerology, see Löwy (1994, 1996).

6 Several have argued against paradigm incommensurability between SMT-CGM and immuno-TOFT. See Marcum (2005, 2009), Malaterre (2007) and Bedessem and Ruphy (2015).

7 See footnote 1 and specifically Löwy (1996), 250–3.

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