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"Triple negative breast cancer": Translational research and the (re) assembling of diseases in post-genomic medicine

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ABSTRACT

The paper examines the debate about the nature and status of "Triple-negative breast cancer", a controversial biomedical entity whose existence illustrates a number of features of post-genomic translational research. The emergence of TNBC is intimately linked to the rise of molecular oncology, and, more generally, to the changing configuration of the life sciences at the turn of the new century. An unprecedented degree of integration of biological and clinical practices has led to the proliferation of bio-clinical entities emerging from translational research. These translations take place between platforms rather than between clinical and laboratory settings. The complexity and heterogeneity of TNBC, its epistemic and technical, biological and clinical dualities, result from its multiple instantiations via different platforms, and from the uneven distribution of biological materials, techniques, and objects across clinical research settings. The fact that TNBC comes in multiple forms, some of which seem to be incompatible or, at least, only partially overlapping, appears to be less a threat to the whole endeavor, than an aspect of an ongoing translational research project. Discussions of translational research that rest on a distinction between basic research and its applications fail to capture the dynamics of this new domain of activity, insofar as application is built-in from the very beginning in the bio-clinical entities that emerge from the translational research domain.

Application is not extrinsic to modern knowledge, it is not just added to some epistemic core; it exerts its action at the very level of concept formation itself; the technical belongs to the essence of the modern sciences themselves.

Rheinberger (2005, p. 324)

1. Introduction

During a June 2012 meeting devoted to National Institutes of Health (NIH) funding, the US Senate Appropriations Committee expressed its concern "about the toll of triple negative breast cancer" [henceforth TNBC] and urged the National Cancer Institute (NCI) to collaborate with other organizations "to help improve treatment and survival rates" (Bin Han Ong, 2012). A decade before, the Committee would most likely have expressed concern over the high rate of breast cancer in general, rather than a specific sub-category of the disease. Recourse to TNBC itself would have been impossible since the disease did not then exist. Its rise to Senate-level prominence was thus relatively swift. A search in PubMed shows that the first article using the term TNBC in its title or abstract did not appear until 2007 when it also entered the public domain, showcased as a national problem in *O, The Oprah Magazine* (Fischer, 2007; see also; Okura, 2010). The year before its PubMed consecration, friends of a young woman diagnosed with TNBC at age 35 had established *The Triple Negative Breast Cancer Foundation.*[1]

While mass media and policy forums reacted promptly to the emergence of this new disease, TNBC's status within biomedicine remained controversial, as evidenced by article titles such as "Triple-negative breast cancer: disease entity or title of convenience?" (Carey, Winer, Viale, Cameron, & Gianni, 2010), or "Triple-negative

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[1] http://www.tnbcfoundation.org/ourstory.htm.

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breast cancer: making the most of a misnomer" (McCarthy, Mitchell, Bilous, Wilcken, & Lindeman, 2012). At a 2013 breast cancer conference, a leading clinical researcher stated categorically that TNBC was not a *bona fide* disease and that speakers should avoid the term … a statement that did not prevent other speakers from using it, with apologies, throughout the conference (fieldnotes, IMPAKT 2013 conference, 2–4 May 2013). At the 2015 edition of that same conference, as part of a session specifically devoted to TNBC, the pathology presenter stated authoritatively that TNBC was "merely an operational term covering a collection of heterogeneous diseases" (fieldnotes, IMPAKT 2015 conference, 7–9 May 2015). Despite questions concerning the definition, status, and in some cases the very existence of TNBC, by 2014 the *Clinicaltrials.gov* website (the U.S. "registry and results database of publicly and privately supported clinical studies of human participants conducted around the world") listed about 240 studies devoted to the disease. Indeed, its widespread clinical use had already prompted a team of European clinicians to publish an article entitled "Triple negative breast cancer: proposals for a *pragmatic definition* and implications for patient management and trial design" (Eiermann et al., 2012; our emphasis). All of this suggests that even in an evidence-based, research-intensive domain such as oncology it remains possible to study and treat diseases that large sectors of the medical community consider misnamed, purely conventional, or even non-existent.

TNBC can be deployed as an object of practical clinical concern *and* as a target of biological investigation (an "epistemic thing"). Consider, for example, the 2013 meeting of the American Society of Clinical Oncology. As evidenced in the meeting abstracts, clinical researchers framed TNBC in multiple clinical and research contexts, and used it to investigate its clinical and pathological behavior, to compare it with other kinds of breast cancer, to calculate the rate of hereditary mutations it harbors, to study the response of its subgroups to traditional and novel ("targeted") therapies, to combine it with other subtypes of breast cancer in order to establish prognostic and predictive subsets, as a starting point for the discovery of yet other breast cancer subgroups, and to investigate its molecular pathways and markers both because they might predict response to therapy *and* in order to unravel TNBC's peculiar biology. In other words, TNBC was deemed an entity worthy of investigation on its own, and as an operational category at the service of a higher calling, the improvement of cancer therapy. Both are ways of saying that TNBC is (clinically) useful, and both are interconnected, as the improvement of cancer therapy these days depends upon knowledge of the mechanisms that inhabit and animate the entities treated.

Research along these lines proceeds unabated at the time of this writing. While some teams continue the search for prognostic and predictive TNBC gene signatures (Liu et al., 2016; Pinto, Araujo, Cardenas, & Morante, 2016), the Intensive Trial of OMIcs in cancer (ITOMIC), a distributed clinical research network centered on the molecular features of cancer, selected metastatic TNBC for its first clinical trial to exemplify the network's "intensive longitudinal monitoring" approach (Blau et al., 2016). As for the Translational Research Network in Oncology (TRIO) — a "worldwide network of 2000 Investigators located in 500 research centers residing in 45 countries spanning 5 continents"[2] — it is looking at repurposing drugs to treat TNBC, i.e. drugs that failed previous tests due to possible problems with the high-throughput methods used in their evaluation (Slamon, quoted in Nailor & Lewis, 2016). In January 2016, the aforementioned *Triple Negative Breast Cancer Foundation* joined forces with *Carol's Crusade for a Cure Foundation* (another private charity devoted to "raising awareness and funding to support organizations at the forefront of [TNBC] research"), and most importantly, with the *American Association for Cancer Research*, to announce a new grant opportunity for "basic, translational, or clinical" research on metastatic TNBC, explaining that "this type of cancer is a particularly aggressive form of breast cancer for which there are no targeted therapies".[3]

These activities, which link practical clinical concerns with biological investigations, take place within a number of programs and networks that, as we just saw, explicitly refer to *translational research* [henceforth TR]. Moreover, several key protagonists of the TNBC domain (e.g., Nielsen, 2010; more on this below) conceive of themselves as translational researchers. A case study of TNBC will thus provide relevant evidence for the investigation of the concrete research practices (as opposed to policy statements) that characterize TR *as defined by the actors themselves*. Since its introduction at the US National Cancer Institute in the early 1990s in connection with the characterization of breast cancer susceptibility genes (BRCA), the term has become ubiquitous in biomedical debates. It is generally taken to refer to major investments in biomedical infrastructures, training, and research to help cross a perceived gap ("the valley of death") between laboratory research and clinical applications (Butler, 2008),[4] but its exact meaning and the practices it entails or ought to entail are open to debate. Several policy reports (for a review, focusing on the UK, see Morgan et al., 2011) and articles, some of which in aptly named journals (e.g., Drolet & Lorenzi, 2011; Mankoff, Brander, Ferrone, & Marincola, 2014) have advocated a number of different means to steer and promote TR, often represented as a flow (unidirectional or bidirectional) between laboratory and clinical settings. Others have advocated initiatives aimed at establishing appropriate infrastructures and reward systems for what they consider as a new research domain (e.g., Hood, 2008). On the more analytical side, researchers have provided scientometric evidence of the emergence of a TR domain as characterized at an aggregate level by distinctive citation and semantic networks (Cambrosio, Keating, Mercier, Lewison, & Mogoutov, 2006; Jones, Cambrosio, & Mogoutov, 2011); they have investigated the dynamics of the organizations involved in TR, for instance the existence of a "hidden research system" in universities and academic hospitals (Lander & Atkinson-Grosjean, 2011), and of scientific-regulatory hybrids (Kohli-Laven, Bourret, Keating, & Cambrosio, 2011); and they have examined how researchers and clinicians situate themselves vis-à-vis the institutionalization of this new sphere of activity (Lander, 2016; Morgan et al., 2011; Vignola-Gagné, 2014).

Critics have argued that TR, as described in the aforementioned contributions, is "merely" a policy object (some would even say: a buzzword), or at best a peculiar set of institutional arrangements, with no distinctive epistemological quality. In other words, old wine in new bottles, as links between bench and bedside have been around for long time, in particular at institutions such as the NIH where research laboratories rub shoulders with a major research hospital. This argument, however, depends on maintaining a dichotomy between organizational and cognitive/epistemic components of biomedicine which is dubious at best (see Cambrosio, Keating, & Nelson, 2014 for a detailed discussion of the relationship between

[2] http://www.cirg.org/html/investigator.html.

[3] http://www.ascopost.com/ViewNews.aspx?nid=35201.

[4] Present-day translational research, and its stated goal of realigning biology and the clinic, can be located in a specific historical conjuncture. While the aftermath of World War II — a period retrospectively referred to as the "golden years" of clinical research (Swazey & Fox, 2004) — saw the emergence of the physician-researcher, the years since have been marked by the rise of molecular biology, and the physicians who had initially launched the clinical research revolution slowly became outnumbered by Ph.D.'s with no clinical experience (Ahrens, 1992).