5 How Cancer Spreads

Reconceptualizing a Disease

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Abstract

Despite tremendous advances in cancer research, a stubborn gap exists between these advances and successful treatments that reduce mortality. One strategic way to address this gap is to model cancer as an infectious disease that we give ourselves. This conceptual maneuver shifts attention from cellular proliferation and tumor growth (how cancer grows) to cellular motility and metastasis (how cancer spreads), and emphasizes properties of cancerous cells that are responsible for the majority of deaths. We use the case of cystic fibrosis as an analogy to show the value of conceptualizing a genetic disease that is recalcitrant to treatment as an infectious disease. One consequence of modeling cancer in this manner is a more direct engagement with the pathological features of cancer's biology and, therefore, it has increased promise for identifying novel clinical applications—the primary goal of translational medicine.

1 Taking Translation Seriously

It is a matter of life or death. Despite 20 years of decreasing death rates in the U.S., cancer remains the second leading cause of death and is expected to overtake heart disease as the leading cause relatively soon (Siegel, Miller, and Jemal 2015). The irony is that cancer researchers have been incredibly productive in terms of publishing research papers and having new drugs approved. In 2012 alone, over 100,000 cancer-related papers were published worldwide. Between 2002 and 2014, the U.S. Food and Drug Administration approved 71 drugs for the treatment of cancers. However, the median gain in survival for those drugs was a mere 2.1 months (Fojo, Mailankody, and Lo 2014). In the U.S., 1.6 million new cases of cancer are diagnosed each year and lead to over 500,000 deaths. A patient's 5-year survival rate is tightly related to how early a cancer is diagnosed. Some cancers, if caught at an early stage, have a 90–100 percent 5-year survival rate (e.g., breast and skin cancers), whereas other cancers have a 5-year survival rate of 2–4% if diagnosed post-metastasis (e.g., pancreatic and lung cancers). What accounts for this stubborn gap between the tremendous advances in cancer biology and a continuing failure to successfully treat cancers beyond the earliest stages of detection?

"Translational research" focuses on the conversion of basic biology discoveries into clinically useful applications. This endeavor has many success

stories, including the polio vaccine and antiretroviral treatments for HIV. In these cases, researchers secured an understanding of the relevant biology contributing to disease pathology, which facilitated clinical application. A robust understanding of the polio virus and our immune system has made it possible to almost eradicate polio globally (The Polio Eradication Initiative 2016). Similarly, an understanding of retrovirus biology and our immune system led to the development of HIV drug regimens that have greatly increased survival rates for HIV patients (Djawe et al. 2015), as well as decreased transmission (Cohen et al. 2011). Why has this kind of success not happened for most forms of cancer?

One potential success story in cancer biology is human papillomavirus (HPV). Nearly 100 percent of all cervical cancers are caused by HPV (Walboomers et al. 1999). Thus, if we could eliminate the virus, then we would stop the cancer. A study published in 2013 estimated that within four years of initiating a program of HPV vaccination, there had been a 56 percent decrease in HPV prevalence in 14–19 year old females despite only 34 percent of females being vaccinated (Markowitz et al. 2013). Longer-term studies have shown protection against HPV strains for 8–9 years after vaccination (Ferris et al. 2014; Naud et al. 2014). Decreasing HPV prevalence has translated directly into decreasing rates of cervical cancer. Though HPV is not yet eradicated, higher rates of vaccination foreshadow the eventual elimination of this cancer.

There is one parallel in cancer biology to the example of HIV treatments. Chronic myeloid leukemia (CML) patients who receive treatment with Imatinib (Gleevec) have an estimated 5-year survival rate of 89 percent (Druker et al. 2006) and a 10-year survival rate of 84 percent (Kalmanti et al. 2015). CML results from a specific chromosomal translocation, which leads to a fusion gene that produces an abnormally active tyrosine kinase (Lugo et al. 1990).[1] Because the resulting kinase is structured slightly differently than other kinases, researchers can precisely target and thus intervene on kinase functionality (Druker et al. 1996). This intervention specificity allows for the treatment's high efficacy. However, the most effective approaches to treating the majority of other cancers are chemotherapy, radiation, and surgery. Although successful in some cases, these treatments are often accompanied by debilitating side effects. Why haven't researchers achieved more effective and less harmful treatment regimens for cancer? These treatments do not engage with features of the biology of cancer related to its causing detrimental health outcomes (i.e., its pathology). Chemotherapy and radiation target dividing cells *generally*, not cancer cells *specifically*.[2] Noncancerous cells are targeted equally in these treatments, and quiescent cancerous cells can evade the toxins, especially after metastasis.[3] The most successful targeted treatments available beyond Imatinib that engage with aspects of the pathology of cancer, such as herceptin for ~15–20% of breast cancers (Ignatiadis et al. 2009), are combined with chemotherapy, which accounts for much of their efficacy (Moja et al. 2012; O'Sullivan et al. 2015; Perez et al. 2014). Researchers must concentrate more attention on how cancer kills in order to achieve successful translations into effective treatments.

How might we facilitate research that can secure a better understanding of the pathology of cancer? How can engagement with relevant aspects of the

biology be spurred so as to generate clinically useful treatment regimens, thereby closing the gap between advances in cancer biology and failures to successfully treat cancers that kill? One way to productively address these questions is to rethink how we understand cancer as a disease. Cancer is currently modeled as a *genetic* disease—a pathology derived from a mutation or other alteration of genomic material (including epigenetic changes). This encourages researchers to focus on identifying the differential expression of particular genes or look for antibodies specific to proteins displayed by cancerous cells (Brennan and Wild 2015). Although not strictly wrong, this conception of cancer misses central aspects of its pathology. Cancer does involve the differential expression of particular genes, but it also involves the differential behavior of cells through complex causal sequences in the contexts of tumor growth and various dimensions of metastasis. Tumor growth dynamics have been studied intensely, acknowledging the importance of unregulated cellular proliferation, but less attention has been given to metastasis (the spread of cancer to other parts of the body), which is what actually kills people in the majority of cases.

Shifting more attention to the dimensions of metastasis (e.g., epithelial–mesenchymal transition, extravasation) has potential for fostering novel clinical applications, though only if we engage with the distinctive biological properties of metastatic cancers (Massagué and Obenauf 2016). A central element of this biology is cellular motility: how cancerous cells invade new environments through transformations of developmental processes. With cellular motility in the foreground, a new conceptualization of cancer emerges that engages directly with aspects of the biology that contribute to its pathology. Instead of primarily scrutinizing how cancer grows (in a tumor), we also must investigate *how cancer spreads* (via metastasis).[4] This spreading from one site to another within a host is analogous to an infection. Reconceptualizing cancer as an infectious disease *that we give to ourselves* suggests novel paths of research that have the potential to translate into successful mitigation strategies.

Our argument is structured as follows. First, we review the aims of cancer translational research and look at how well current conceptions of cancer match those aims. Next, we discuss the common distinction between genetic and infectious diseases and show how this breaks down in the context of cystic fibrosis. Cystic fibrosis is both a genetic and an infectious disease, and its pathological facets require taking the latter into account explicitly. This case study provides a segue to modeling cancer as an infection in addition to thinking about it as a genetic disease. After detailing this conception, we explore potential payoffs for cancer translational research, especially the application of approaches from epidemiology and ecology. We conclude that reflecting on how cancer is conceptualized in research can have direct consequences for investigation aimed at the discovery of new clinical interventions.

2 Idealized Models and Cancer Translational Research

A scientific community often has several distinct conceptualizations or models of the natural phenomena it attempts to investigate, manipulate, and explain. These are

guided by a variety of assumptions embedded in, and sometimes constitutive of, the pertinent group of researchers. Multiple conceptualizations of natural phenomena can be maintained in investigative communities, such as treating physical matter as discrete particles, rigid bodies, or continuous masses (Wilson 2013). Biologists treat the interior space of a cell as if it was relatively empty even though intracellular space is known to be crowded (Ellis 2001). Idealization—a reasoning strategy that scientists use to describe or model that purposefully departs from features known to be present in nature (Jones 2005; Weisberg 2007)—plays a central role in these conceptions by facilitating the investigation of specific properties and making it difficult, if not impossible, to study others. For example, matter is composed of atoms and therefore not strictly continuous. Likewise, sometimes biologists ignore variation in the timing of developmental events to produce normal stages that facilitate studying ontogeny (Love 2010). Idealized models always combine distinctive strengths alongside latent weaknesses. Thus, idealizations should be closely matched with the aims of inquiry and coordinated with particular properties of interest for any natural phenomenon being investigated (see Plutynski, this volume).

With the introduction of the translational research initiative at the U.S. National Institutes of Health (NIH) in the 2000s, then-director Elias Zerhouni encouraged the development of "novel approaches" that can "be truly transforming for human health" (Zerhouni 2005, p. 1621). This led to the NIH Roadmap for Medical Research (Zerhouni 2003) and a reorganization of the NIH in 2012 to accommodate the addition of the National Center for Advancing Translational Science (Wadman 2011). The aims of translational research revolve around the identification and application of novel clinical treatments that benefit human health. In terms of cancer, this initiative has led to programs like The Cancer Genome Atlas to track key molecular changes that occur in various cancers (National Cancer Institute 2016a), and the formation of Specialized Programs of Research Excellence to serve as collaborative interdisciplinary teams with projects "that will result in new and diverse approaches to the prevention, early detection, diagnosis and treatment of human cancers" (National Cancer Institute 2016b).

These programs tend to presume a particular model of cancer as a natural phenomenon: cancer as a *genetic* disease caused by alterations in the molecular structure and function of the genome (Brennan and Wild 2015). As a consequence, researchers focus on those properties that are salient in this conception, such as the differential expression of particular genes or DNA sequence variants that serve as molecular signatures of tumor formation and growth. They also concentrate on those properties for a particular time in the sequence of cancer progression: early detection and prevention.

However, with respect to the goals of translational research, there are many reasons not to rely on early detection and prevention alone in efforts to eliminate cancer. For one, many tumors (or what is diagnosed as "cancer"[5]) will grow but remain localized, inflicting no harm on the individual. Identification of a growing tumor conjoined with the fear of its spreading can lead to unnecessary surgeries, such as thyroidectomies, mastectomies, and prostatectomies (Scudellari 2015). In the case of breast cancer, early treatment via chemotherapy, radiotherapy, or

mastectomy does not reduce the risk of breast cancer–specific mortality; patients who undergo early treatment of ductal carcinoma *in situ* (stage 0 breast cancer) are just as likely to die of breast cancer as women in general society (Narod et al. 2015). Additionally, some cancers are identified via molecular proxies (cf. Nathan, this volume), such as elevated levels of prostate-specific antigen (PSA) in screening for prostate cancer, which can encourage more invasive tests, like prostate biopsies (Prasad, Lenzer, and Newman 2015). In these types of cases, attempts to detect cancer early are more likely to harm than to help the individual due to the high rate of false positives. Furthermore, early screening can sometimes lead to reduced specific mortality (e.g., dying from prostate cancer), but not reduced overall mortality (e.g., dying from something else just as early or earlier).

Our intention is not to discourage attending to early detection and cancer prevention in clinical settings. However, even if screening and detection worked better, they would never catch all cases early. We still need a way to treat cancers that have moved beyond the early stages of tumor growth and into the dimensions of metastasis (Massagué and Obenauf 2016). And since metastasis is the pathological aspect of cancer—essentially the causative factor of death—we need approaches that enhance the ability of researchers to understand, detect, prevent, and treat these later stages of cancer. We need a conceptualization of cancer that facilitates investigating specific properties that make it pathological; we need a model that is more closely matched with the aims of inquiry (i.e., translational research). Only then will we be positioned to better identify novel and effective treatment regimens for the metastatic dimensions of cancer.

Metastasis is remarkably different from tumorigenesis. Early in the process, unregulated and uncontrolled tumor growth are the greatest concerns (*how cancer grows*). Later, the transformation, movement, and recolonization of cancerous cells move to the foreground (*how cancer spreads*). Tumorigenesis and metastasis exhibit different environmental contexts, thus suggesting distinct ecological dynamics as well as different cellular properties, thereby highlighting different developmental processes. However, if the aims of inquiry are translational, and pathological aspects of cancer are concentrated largely in the metastatic phase (Massagué and Obenauf 2016), then we should reconceptualize cancer accordingly to facilitate investigation of those properties pertaining to metastasis, such as cell motility. An idealized conception of cancer that makes properties appearing at these later temporal stages of cancer progression more salient is desirable. An analogy from epidemiology is apt: treat metastasis as a kind of infection whereby cells of a single individual propagate out to new locations in the body. Instead of focusing primarily on molecular genetic markers of tumorigenesis, we should also investigate the properties underlying the infectious propagation. The advantages of this type of idealization are more readily apparent in an altogether different case: cystic fibrosis.

3 Genetic *and* Infectious Diseases: Illumination from Cystic Fibrosis

Many, if not most, diseases are now conceptualized in terms of molecular deficiencies and labeled "genetic" diseases (Darrason, this volume). This is

most notable for those displaying a Mendelian pattern of inheritance, such as Phenylketonuria, due to a deficiency in phenylalanine hydroxylase (Blau, van Spronsen, and Levy 2010), or Huntington's disease, resulting from an autosomally dominant mutation in the *huntingtin* gene (Walker 2007). Diseases showing more complex, non-Mendelian inheritance patterns (van Heyningen and Yeyati 2004) are also conceptualized in terms of alterations in normal gene expression or some other molecular activity (e.g., abnormal protein folding). This conceptualization focuses on intrinsic properties of the individual and is reflected in our language: we "have" genetic diseases. By way of contrast, a different category of diseases consists of those associated with specific microbial agents, such as *Mycobacterium tuberculosis*. Patterns of inheritance are not in view for most infectious diseases; instead, the concern is about their *transmission*. This conceptualization focuses on the properties of microbes extrinsic to the individual: we "get" or "catch" infectious diseases. Therefore, standard categorizations of disease typically distinguish genetic diseases from infectious diseases. However, there are some diseases that blur the line.

Cystic fibrosis (CF) is characterized by thick mucus buildup that restricts the function of the lungs and airways. It originates due to mutations in a single gene, *cystic fibrosis transmembrane conductance regulator* (*CFTR*), which produces a transmembrane channel protein that regulates chloride ion transport. In cells that generate water-based secretions (e.g., mucus, sweat, saliva, or tears), the regulation of chloride ions is critical for moving water in and out of tissues. Because of this causal etiology, and the fact that it displays an autosomally recessive Mendelian inheritance pattern, CF is routinely labeled a *genetic* disease. However, the pathological aspects of CF do not derive primarily from a buildup of mucus. CF is also characterized by chronic infections due to multiple microbial species, especially *Pseudomonas aeruginosa* and *Burkholderia cepacia*. These infections are transmissible from patient to patient and comprise an essential part of the negative health effects associated with CF (Sun et al. 1995; Fothergill, Walshaw, and Winstanley 2012). Thus, CF is also an *infectious* disease (Lyczak, Cannon, and Pier 2002; Sibley, Rabin, and Surette 2006).

If the goal is to adequately address CF as a disease, then conceptualizing it only, or even primarily, as a genetic disease will lead to clinical frustration. CF has been stubbornly difficult to treat for a genetic disease where we have pinpointed the specific gene and that displays a relatively simple inheritance pattern; gene therapies continue to be disappointing (Alton et al. 2015). Importantly, this does not mean that conceptualizing CF as a genetic disease will prevent all research advances into aspects of its basic biology. Conceptualizations are idealized models in the sense of purposefully neglecting known features of natural phenomena in order to facilitate investigation of specific properties. Researchers know that bacterial infections are a key component of the disease etiology of CF, but the genetic disease conceptualization ignores these for the purpose of focusing on molecular genetic mechanisms that break down in the early stages of the condition. Models should be closely matched with the aims of inquiry and coordinated with particular properties of interest for a natural phenomenon being

investigated. Conceptualizing CF as an infectious disease is an idealization that intentionally neglects the breakdown in chloride ion transport regulation due to a mutated transmembrane protein. However, it is an idealization that facilitates the investigation of specific properties of CF related to its pathology.

The realization that CF's complex pathogenicity involves infection has yielded multiple advances in treatment. CF was originally described as a pathological condition of the pancreas ("steatorrhea"; Andersen 1938; Parmelee 1935). Poor pancreatic function often resulted in death due to malnutrition for many patients, but it also would lead to other conditions, such as diabetes (O'Sullivan and Freedman 2009). CF was long considered a pediatric disease because a majority of individuals with the condition died in their first year of life. At this time, the latest observed age of death was 14.5 years, but the average age of death was 1 year (Parmelee 1935).

By the 1950s, the characterization of CF had expanded to encompass general exocrine gland dysfunction, which included pancreatic deficiencies, susceptibility to chronic bronchitis, and increased electrolytes in the sweat (Andersen 1958). Because pancreatic dysfunction could be treated with pancreatin substitution therapy, the usual cause of death in those affected was respiratory infection. By then, mortality was not occurring until between 3 and 5 years of age, and many were living through their teenage years. The introduction of penicillin was a key part of this improved lifespan (Andersen 1958). Now patients live well into adulthood; the median survival age more than doubled between 1969 and 2001, from 14 years to 30 years (Döring and Hoiby 2004). It has been estimated that patients born in 2000 will live into their 50s (Dodge et al. 2007). This is due to particular antibiotics, such as sulfonamides, tetracyclines, and carbenicillin, which came into use from the 1940s through the 1970s (Fernald and Boat 1987). Patients with specific infection types (*P. aeruginosa*, *B. cepacia* complex, or MRSA infections) are encouraged to be seen in separate clinics or at separate times than other patients to reduce the chances of cross-infection (Kerem et al. 2005).

Conceptualizing CF as an infectious disease has encouraged increased attention to the evolutionary dynamics of its microbial pathogens. Many researchers have analyzed the long-term evolution of *P. aeruginosa* in respiratory infections to understand how it can adapt to the dynamic lung environment of CF patients. A recent study looked at the immediate impact of various treatments on *P. aeruginosa* in a 34-year old female patient over a 1-year period (Diaz Caballero et al. 2015). Sputum samples were obtained longitudinally and correlated with the prescribed antibiotic treatments (12 samples over a 1-year period). It was discovered that *P. aeruginosa* populations evolved quickly in stressful environments (e.g., in response to antimicrobial treatments). There were genomic signs of recurrent selective sweeps and many indicators of parallel adaptation at loci for antibiotic resistance. However, the advantage of these alleles was dependent on specific antibiotic environments; an allele was beneficial during certain antibiotic treatments but disadvantageous in others. Understanding short-term evolutionary dynamics is critical to deciphering the relationships between treatment regimes and clinical success. Given that treatment regimes for CF usually

include long-term antibiotics to prevent or control infections (along with various methods for loosening mucus build up), conceptualizing CF as an infectious disease helps to accent how microbes evolve in the host's lungs and thereby intensify the pathology of CF. Identifying and characterizing these features increases the potential for translating research findings into effective clinical treatments.

The trajectory of research on CF shows the differential value of distinct disease conceptualizations. CF can be modeled as either genetic or infectious, and each idealization serves the purpose of securing a better understanding of the relevant features of its basic biology. Since each conceptualization combines distinctive strengths (in terms of the specific properties in view) and latent weakness (in terms of those features neglected or ignored), the important question is not whether one conceptualization is better than the other but rather what end or goal they serve. Given that the pathological dimensions of CF arise later in the disease progression due to evolutionarily dynamic populations of microbes, a conceptualization of CF as infectious is currently better suited to identifying clinically relevant and effective treatments. Recent research amply supports this claim.

Three key lessons emerge from recognizing that we can model CF as either a genetic or infectious disease. The first is that a conceptualization should be well matched to the aims of inquiry. If the aims of inquiry are translational, then the disease conceptualization should make salient those properties that contribute to pathology. Knowing these features of the basic biology for a particular disease are most relevant to finding effective clinical treatments. Second, the case of CF (and what we have already noted for cancer) suggests that conceptualizations of a disease depend on where one concentrates in its temporal progression. The initial stages of CF are better construed as a genetic disease, where the buildup of mucus is a function of mutations in *CFTR*. The later stages of CF are better construed as an infectious disease, in which different bacterial communities invade under the conditions of excess mucus and progressively become better adapted to the host's immune defenses (and therefore more pathological). The evolutionary dynamics that yield this progressive adaptation are germane for fine tuning treatment regimens to increase their effectiveness. Finally, shifting from a model of CF as a genetic disease to CF as an infectious disease alters how we view causal responsibility within the disease progression. At the outset, consistent with modeling cancer as a genetic disease, the responsibility is located in the deficient molecular component, which leads to the mucus buildup in the lungs. However, later in the temporal progression of CF, the responsibility is located in the bacterial species invading the environment of the lungs and ultimately producing pathogenic effects in the host.

The three lessons—matching conceptualizations to aims of inquiry, focusing on particular segments in the temporal progression of a disease, and isolating where causal responsibility lies for pathology—can be encapsulated as we segue to explicitly conceptualizing cancer as an infectious disease. For cancer translational research, a conceptualization of the disease should be matched to finding effective clinical treatments beyond the earliest stages of detection, which means later stages of its progression (i.e., metastatic dimensions), where

the relevant causal responsibility lies with motile cells invading and adapting to new areas of the body rather than with mutations that initiate tumor formation by upsetting cell cycle regulation.

4 Conceptualizing Cancer as an Infection

Cancer is often thought to be the classic example of a genetic disease. Cancers start with a mutation (either spontaneous or induced), followed by unrestricted proliferation to generate a mass of cells (i.e., a tumor), and then, with variable frequency, transition to disseminating cancerous cells to other locations in the body (i.e., metastasis), which usually results in death. Because a cancer starts and ends in an individual who harbors a pertinent genetic mutation, it seems odd to think of cancer as an infectious disease. You (seemingly) cannot "catch" cancer. The pathology is not transmitted from one individual to another, at least not typically. There are cases of transmissible cancer, such as in clams or dogs (Metzger et al. 2015; Murchison 2009). Perhaps the most famous of these has been observed in Tasmanian devils.

The Tasmanian devil is facing extinction due to devil tumor facial disease (DTFD). DTFD is transmitted cellularly though facial bites while fighting. The cells grow rapidly, spreading throughout the face and neck and then metastasize through the lymph nodes to reach distant organs (Loh et al. 2006). Within months, the cancer's spread leads to death. DTFD shows all of the conventional signs of cancer: unrestricted growth of cells that spread throughout the body (or metastasize) and lead to death. However, molecular analyses of multiple individuals have demonstrated that the cancer is clonal and monophyletic, arising from a single outbreak of Schwann cell origin. Therefore, it is not initiated genetically by a mutation in the affected individual. The cancer is transmitted as an allograft (i.e., as a distinct tissue); cancerous cells between individuals exhibit more similarity than the cancer does to the cells of its host (Murchison et al. 2010). The transmissibility of DFTD is associated with a decreased immune response. Since the tumor is a graft from a different individual, it should be recognized as foreign by the immune system, but it is not (Siddle et al. 2007). Again, this behavior tightly parallels what we would expect for an infectious disease.

Despite their intrinsically fascinating status, DFTD and other transmissible cancers are usually considered exceptions to the rule. In part, this is because the majority of cancer cases thus far studied do not involve any transmission of the pathology from one individual to another. However, if we set aside the criterion of transmission from one "distinct" individual to another and concentrate on how cancer spatially spreads through the various dimensions of metastasis, cancer is quite analogous to a transmissible disease that moves from one area or tissue in an individual to another. Subsequent to tumor origination and growth, it behaves like an infectious disease that we give ourselves, or that one part of an individual gives to other parts. This conceptualization concentrates our attention on how cancerous cells move from one location to another, from the original tumor to establishment elsewhere in the body (Massagué and Obenauf 2016), which is how cancer primarily kills individuals.

Recall our three lessons from the case of CF. First, conceptualizations of a disease should be suited to finding effective clinical treatments by drawing attention to specific properties that contribute to a disease's pathology. Second, a conceptualization is keyed to a particular segment of the temporal progression of a disease. Third, any conceptualization highlights particular types of causal responsibility for a disease. Conceptualizing cancer as an infectious disease focuses on the later stages of its progression (i.e., metastatic dimensions), rather than earlier stages where a molecular characterization of unregulated cellular proliferation in terms of genetic mutations is apt. These later stages of cancer's progression are where the specific, pathological properties of the disease are largely confined. Metastasis is the primary killer, not tumor growth. And causal responsibility attaches to the property of cell motility whereby tumor cells detach and invade new environments (i.e., other locations in the body) through a variety of developmental transformations (e.g., epithelial–mesenchymal transition or intravasation), as well as adapt to different conditions within the body (Massagué and Obenauf 2016). An idealized model of cancer as an infectious disease appears well suited to the aims of cancer translational research.

Once this conceptualization of cancer is in view, it encourages us to scrutinize in more detail the specific properties made salient in the model. For example, cancerous cells exhibit distinct evolutionary dynamics in the host individual in the later stages of progression (i.e., the metastatic dimensions), in part to evade the immune system, which is being encountered in different ways as these cells migrate into new environments of the body. The fallible engagement of the immune system helps to account for the existence of remission phases, similar to what we see for other infectious diseases (e.g., HIV), as well as resistance to treatments. Although the cancerous cells that evolve to evade the host immune system or become resistant to treatment are not microbes (as in CF), the cellular behavior is remarkably similar.

The first similarity is that both cancer and infectious diseases have underlying clonal evolutionary dynamics that are specific to that individual and depend on a variety of local circumstances. For example, there are episodes of periodic selection and clonal interference that regularly affect populations of cancerous cells and infectious agents (Nowell 1976; Diaz Caballero et al. 2015), but these exhibit characteristics unique to each particular patient, such as how rapidly their pathological effects become manifested due to individual differences in immune response. A second similarity is that there will be convergent evolution of cancerous cells and infectious agents as different functional niches are filled, leading to the appearance of homogeneity across and between cancers and infectious diseases, especially on longer time scales and for analyses at higher levels of organization. This convergence is what yields typical ranges of disease progression for particular forms of cancers and transmissible infections. However, historical contingency and differences in the local ecologies of each individual will lead to variation in disease progression and thus the need for different treatment plans between individuals. The order and frequency of treatments are important for understanding progression and predicting the evolution of a cancer

(Greaves and Maley 2012; Diaz Caballero et al. 2015). Different treatments will stress a cancer in different ways, leading to differential growth and variegated propagation among various clones in the population. Thus, analyses at lower levels of organization and across shorter time scales will often reveal heterogeneity that is relevant to effective treatments, especially for the dimensions of metastasis (Massagué and Obenauf 2016).

A third similarity between cancer and infectious diseases is that both depend on decreased immune system function for disease persistence and progression. In the case of CF, as populations of *P. aeruginosa* adapt to the lungs of an affected individual, immune system function decreases, which allows for the persistence of the bacterial infection and nurtures its evolution. With DFTD, the contracted cancerous cells can only persist in the presence of a depressed immune system. Although mutations occur frequently in somatic cells, cancers do not occur as a necessary result because the immune system recognizes cells harboring these mutations as abnormal and eliminates them. Cancerous cells are able to evade the immune system and proliferate. This principle is what immunotherapies aim to leverage: increase the activity of the immune system so as to better detect and destroy abnormal and potentially cancerous cells. However, less attention has been given to how the immune system might detect and destroy circulating tumor cells post-metastasis. For example, epithelial–mesenchymal transition may not be required for metastasis in lung cancers, but when this transition does occur, there is an increase in drug resistance (Fischer et al. 2015). Modeling cancer as an infectious disease points us toward immunotherapies, which are receiving increasing attention (see below, Section 5), though we might have arrived there earlier.[6] Drawing an analogy between CF and cancer illustrates the value of conceptualizing cancer as an infection; it directs our attention to the relevant biological features for identifying novel clinical applications.

5 Payoff: Conceptual Reflection Leads to Research that Saves Lives

The reconceptualization of cancer as an infectious disease reminds us starkly of the primary source of cancer mortality—metastasis. This reorients the usual success story told about cancer research. Every January, the American Cancer Society, the Centers for Disease Control and Prevention, the National Cancer Institute, and the North American Association of Central Cancer Registries jointly release the latest statistics surrounding cancer. These annual reports show that death rates continue to decline, as they have for the last 20 years (see, e.g., Siegel, Miller, and Jemal 2015). However, these reports lump together all cases of the same type of cancer. For example, the 2015 report shows that lung cancer survival rates are improving. This is almost exclusively because of early detection through screening rather than because of better treatments. The 5-year survival rate for lung cancer if diagnosed early is over 50 percent, but the 5-year survival rate for lung cancer if diagnosed post-metastasis is 2 percent. Unfortunately, more than half of all cases are not diagnosed until the cancer

has metastasized. While new molecular methods for early detection certainly count as contributions to translational medicine, the pathogenicity of metastasis is sobering; the need to achieve an understanding of metastasis that will translate into more effective clinical treatments becomes readily apparent.

That an idealized model of cancer as an infectious disease can change how research programs are interpreted is perhaps not surprising. For example, with cancer modeled as an infectious disease, immunotherapies move into the spotlight for addressing metastasis. If the idealized model changes how research programs proceed, then the proposal is more substantial. We think this is the payoff of conceptual reflection on how we think about cancer as a natural phenomenon; in a very real sense, it could lead to saved lives. Research that concentrates on achieving a better understanding of cancer's sources of mortality as a consequence of this reconceptualization is poised to make a big clinical difference. Before isolating these effective treatments, changes in the research programs need to unfold. We see at least two domains where conceptualizing cancer as an infectious disease could help redirect aspects of cancer translational research: epidemiology and ecology.

Cancer epidemiologists typically study trends in incidence and mortality rates with the goal of identifying risk factors that can be used in screening and prevention practices. This is how tobacco and asbestos were identified as risk factors for cancer. Similarly, epidemiologists track the spread of diseases via molecular markers, such as new subtypes of influenza that are measured globally on an annual basis (cf. Russo and Vineis, this volume). Identification of subtypes is critical for influenza vaccine development; even a partial misprediction of the annual type results in suboptimal vaccines (Flannery et al. 2015; Ohmit et al. 2014; Pebody et al. 2013). Tuberculosis is another example; strains of *Mycobacterium tuberculosis* can be identified to determine the proportion of cases due to new infections versus reactivation of previous infections. Thus, researchers can identify which strains are more or less able to spread through populations (Foxman and Riley 2001). These examples highlight three familiar aspects associated with infectious disease: pathogen infectiousness, host susceptibility, and host–pathogen interactions. Influenza is one of the most infectious pathogens but is readily cleared by otherwise healthy individuals. *M. tuberculosis* is far less infectious, but chronic and lethal infections are commonplace without antibiotic treatment. In both cases, there is substantial variation in host susceptibility among individuals.

While some of these insights have been incorporated into cancer research, this has mostly occurred in a piecemeal fashion. Cancer treatment outcomes are negatively correlated with the degree of metastatic spread, which has encouraged attempts to systematize the stages of cancer (Bülzebruck et al. 1992; Bundred 2001). Ideally, such a systemization would provide better approaches to screening, estimates of survival, and therapy. However, debates about approaches to all three of these are extremely contentious (Hari et al. 2013; Miller et al. 2014; Pace and Keating 2014). This is largely because epidemiological perspectives are not well integrated into cancer medicine. Although there are now very sophisticated mathematical models (Kam, Rejniak, and Anderson 2012), their clinical relevance has been modest. The explicit incorporation of mathematical models and

epidemiological perspectives into translational medicine more broadly should provide clarity about the sources of cancer mortality (e.g., through more precise delineations of resistance to treatment at distinct stages). Recent studies have identified genetic variation among cancer cells as a possible indicator of cancer aggressiveness and persistence (Lauren et al. 2006; Park et al. 2010). Epidemiological studies of many infectious diseases over the past half-century show similar correlations (Bloom 1979; Demerec 1948; Webster et al. 1992). If cancer had been conceptualized as an infectious disease, this could have provided a faster pathway to discovering potential strategies of treatment. More generally, cancer translational research has not focused on the origin of genetic variation beyond assuming it arises from mutation (Burrell et al. 2013). Genetic variation—a pivotal element of infectious disease epidemiology—is the ultimate source of cancer recurrence after therapy.

Researchers have long recognized that individuals vary in their cancer susceptibility and survivorship, but the emphasis was primarily on mutations in specific genes or behavioral and environmental factors that promote differences in cancer initiation and spread (Danaei et al. 2005; Nigro et al. 1989). Until recently, there was much less interest in the host environment. Individuals vary in their susceptibility to infectious diseases, and these differences have provided insights for understanding disease mechanisms and facilitating the development of treatments (e.g., partial immunity to HIV). Perhaps of greater value is the recognition that the infectiousness of pathogens and susceptibility of hosts can *interact*. Some individuals are relatively unsusceptible to pathogens that are lethal to others. Longitudinal and comparative observations for cancer incidence and progression have provided clues to individualized treatments, but identifying differential susceptibility of distinct tissues within the same individual merits further investigation. Comparisons within and between individuals with specific cancers that progressed to metastasis in preferred locations with those individuals whose tumor (of the same type) stayed benign or exhibited different patterns of metastasis could illuminate the nature of these interactions. Scrutinizing instances where progression is anticipated but not observed (especially in cases of spontaneous remission) is likely to generate translational insights. Epidemiological approaches premised on studying cancer as an infectious disease will improve our understanding of the dynamics of its spread and yield insights relevant to effective treatment regimes that reduce mortality beyond early detection.

A focus on epidemiology naturally presages the relevance of ecological perspectives to the study of cancer as an infectious disease. The probability of transmission (or propensity to spread), contact rates between individuals (or between parts of the body), and the susceptibility of the next host (or organ system) are relevant to infectious disease and metastatic cancers alike. Although epidemiological models are powerful approaches to formulating hypotheses about patterns of contagion and pertinent risk factors, the actual mechanisms involve ecological interactions (Merlo et al. 2006). For example, cells (or clusters of cells) constantly break off from tumors and move through the circulatory system, but only a small fraction of those clusters successfully seed new tumors

at a distant location (Aceto et al. 2014; Massagué and Obenauf 2016). "Seed versus soil" views of metastasis suggest that cells (the seeds) must match characteristics of the new environment to be occupied (the soil) in order for metastases to be successful. Models that include relevant ecological interactions provide mechanistic details about both matches and mismatches to explain phenomena like preferred metastatic destinations.

The application of concepts from infectious disease biology can help in identifying the primary characteristics of environments that permit metastasis. For example, what properties are pertinent to the susceptibility of the new host? Which tissues are more likely to allow for the successful planting of metastases, and why? In parallel with the infectious disease examples discussed earlier, susceptible tissues are likely found in systems that have lessened immune responses. Organ systems with stronger immune responses will recognize cancerous cells and eliminate them. In cases of organotropic metastasis, where there are special affinities between the tissue of tumor origination and likely sites of spread (e.g., lung, liver, and brain), general immune reactions to cancerous cells may be subverted by a distinct molecular indicator, such as exosomes containing distinctive suites of integrins (Hoshino et al. 2015). Knowing these "ecological" interactions of host immune responses (or lack thereof) is critical for developing novel clinical interventions.

Although cancer research has increasingly focused on the role of the immune system, especially with the rise of immunotherapy (Restifo, Dudley, and Rosenberg 2012), progress on this front could have been achieved earlier and in a less haphazard fashion by recognizing general ecological principles that apply to the infectious aspects of cancer. For example, what are the contact rates between cancer cells and different regions of the body? What kind of contact is the most important for successful metastasis (e.g., intermittent, repeated, or constant)? Environments with lots of cell movement permit mass-action dynamics where all cells have access to resources, which allows for the invasion of cheaters or cells that exploit resources without contributing. On the other hand, environments that are spatially structured severely limit the ability of cheaters to invade (Chao and Levin 1981; Escalante et al. 2015; Greig and Travisano 2004; Greig and Travisano 2008; Travisano and Velicer 2004). Thus, we would expect tissues with more spatial structure to be more resistant to the spread of cancer, whereas tissues with less spatial structure should be more permissive to metastasis. Addressing these ecological components is essential for fighting infectious diseases and therefore must be included in mitigating the spread of cancers as well.

Ecological perspectives on cancer that incorporate interactive dynamics and environmental context are not new (see. e.g., Gatenby, Brown, and Vincent 2009; Kareva 2015; Merlo et al. 2006). Nowell's well-known clonal evolution model had ecological elements, even if not explicitly stated (Nowell 1976). Most of these perspectives come in one of two forms. First, there are reviews that attempt to apply as many ecological (and evolutionary) concepts as possible to cancer as a system. Everything ranging from competition (for space and resources) and niche construction (changes in the microenvironment) to predation (via the immune system) and ecological succession (progression through the stages of cancer) are

discussed (Kareva 2015; Merlo et al. 2006). The second form is to highlight similarities with already familiar systems, such as drawing analogies between cancer and invasive species or pests (Gatenby 2009; Gatenby, Brown, and Vincent 2009), or the evolution of cancer and the evolution of a new species (Kaznatcheev 2014). Our goal is not to add more ecological concepts or analogous systems to the list but to narrow the list to idealized models that will lead to novel translational results. This means applying select concepts to cancer biology so as to understand why and how metastasis occurs. That cells moving through the circulatory system are similar to organisms migrating is interesting, but can an analogy to migration yield novel treatments? The discussion of mass-action dynamics and cheating suggests an affirmative answer, though more work is needed to elucidate the details. As with any analogy, cancer stages and ecological succession have many similarities, but also many differences. Comparing metastasis to ecological succession highlights that they share a sequence of relatively predictable events (Kareva 2015). However, the predicted progression would be linear and end when the climax or stable state is reached, whereas the processes relevant to cancer are more cyclical and involve diverse environments (Divoli et al. 2011).[7] An idealized model based on the similarities should be matched to the aims of inquiry. If the aim is to understand the pathology of metastasis, ecological succession might not be the best analogy for identifying effective clinical treatments.

6 Conclusion

Cancer translational research is making notable progress, but that progress is almost entirely through the vehicle of prevention and early detection from screening practices. There is a gap between these advances in cancer biology and our ability to treat cancers beyond the earliest stages of detection. We have argued that one way to address this gap is through reconceptualizing cancer as an infectious disease that we give ourselves. Most research programs model cancer as a genetic disease and focus on the early stages of how cancer grows. Both of these conceptualizations are idealized models that facilitate the investigation of some properties and elide the study of others. If the aims of inquiry are guided by the demands of identifying effective clinical treatments (i.e., translational research), then an idealized model that accents the pathological properties of cancer is a necessity. These pathological properties are almost universally located in the metastatic dimensions of cancer.

Support for switching from a genetic disease conceptualization to an infectious disease conceptualization derives from the case of CF, where increasing scrutiny of microbial infections in the later stages of disease progression has yielded significant advances in patient treatment. Additionally, the dynamics of transmissible cancers, such as DFTD, assist us in reorienting our conception of cancer as infectious despite most cases of cancer being confined to a single individual. Cancerous cells spread to new locations in an individual's body just as a pathogen can spread to new hosts. This conceptual move fixes our attention on the relevant biological features of metastatic cancers that should help translational research meet its goals. This includes novel angles for cancer research programs, such as the application

of epidemiological and ecological approaches, which are both sources for inspiration in finding shared patterns of transmission dynamics and isolating mechanistic principles that will predict the direction and rate of metastasis, thereby nurturing novel clinical applications. It is noteworthy that this exemplifies the repeated call for cross-disciplinary approaches to cancer (e.g., Ogden 2015).

In matters of life and death, conceptual reflection is usually deemed a luxury. However, stepping back to evaluate how our idealized models do or do not contribute to the goals of translational medicine may be indispensable for identifying a suite of new treatment regimens that effectively deal with metastatic cancers. Only then will we be positioned strategically to understand the pathogenic properties of cancer's biology and thereby close the gap between major research advances and a paucity of treatments that save lives.

Notes

1 In noncancerous individuals, the genes *c-abl* and *brc* are separated spatially on different chromosomes. CML occurs when the two chromosomes break and fuse together at the location of the two genes forming the *brc-abl* gene. This new version of the gene produces an enzyme (a tyrosine kinase) that is constitutively active, leading to excess differentiation of blood stem cells into white blood cells (Sawyers 1999).
2 Immunotherapies are an attempt to secure a general treatment that will target cancerous cells by harnessing the specificity of our adaptive immune system.
3 Some chemotherapies might target cancerous cells more than noncancerous cells because the former upregulate normal processes. However, because these processes occur in normal cells, they also will be affected. For example, the chemotherapy drug cisplatin induces apoptosis by interfering with DNA repair, which operates in normal cells but is more active in cancerous cells (Dasari and Bernard 2014).
4 It is important to emphasize that many biologists work on cell motility and cancer metastasis. Our argument is that modeling cancer in a particular way encourages investigating some properties rather than others (see below, Section 2). Conceptualizing cancer as an infectious disease shifts attention away from tumor origination toward cancerous cell propagation. This does not devalue research focused on finding ways to eliminate nonmetastatic tumors.
5 *Cancer* and *tumor* are frequently used interchangeably, but the label *tumor* is reserved for uncontrolled growth, and *cancer* refers to the spread of the cells to other locations (National Cancer Institute 2015). The term *cancer* covers both solid (e.g., breast and prostate cancers) and liquid cancers (e.g., leukemias and lymphomas). Our discussion focuses only on solid cancers.
6 The "father of present day immunotherapy," William B. Coley, treated inoperable sarcoma by injection of bacteria in the early 1900s. This treatment was based on the observation that cancer regressions were associated with bacterial infections called erysipelas (Wiemann and Starnes 1994).
7 Kareva admits the analogy does not hold exactly because the patient usually dies when the climax state is reached, but this is a different application of ecological succession than our view suggests.

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