Infection, Genetics and Evolution 39 (2016) 293–303

Contents lists available at ScienceDirect

Infection, Genetics and Evolution

journal homepage: www.elsevier.com/locate/meegid

Review

The evolutionary ecology of transmissible cancers

Beata Ujvari [a,*,1], Robert A. Gatenby [b,1], Frédéric Thomas [c,1]

[a] Deakin University, Geelong, School of Life and Environmental Sciences, Centre for Integrative Ecology, Waurn Ponds, Vic 3216, Australia
[b] Department of Radiology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL 33612, USA
[c] CREEC/MIVEGEC, UMR IRD/CNRS/UM 5290, Montpellier, France

ARTICLE INFO

Article history:
Received 5 November 2015
Received in revised form 4 February 2016
Accepted 5 February 2016
Available online 6 February 2016

Keywords:
Cancer
Transmissible cancer
Host–parasite interactions
Infection
Evolution

ABSTRACT

Transmissible tumours, while rare, present a fascinating opportunity to examine the evolutionary dynamics of cancer as both an infectious agent and an exotic, invasive species. Only three naturally-occurring transmissible cancers have been observed so far in the wild: Tasmanian devil facial tumour diseases, canine transmissible venereal tumour, and clam leukaemia. Here, we define four conditions that are necessary and sufficient for direct passage of cancer cells between either vertebrate or invertebrate hosts. Successful transmission requires environment and behaviours that facilitate transfer of tumour cells between hosts including: tumour tissue properties that promote shedding of large numbers of malignant cells, tumour cell plasticity that permits their survival during transmission and growth in a new host, and a 'permissible' host or host tissue. This rare confluence of multiple host- and tumour cell-traits both explains the rarity of tumour cell transmission and provides novel insights into the dynamics that both promote and constrain their growth.

Contents

* Corresponding author at: Deakin University, Geelong, School of Life and Environmental Sciences, Centre for Integrative Ecology, Waurn Ponds, Vic 3216, Australia.
E-mail address: beata.ujvari@deakin.edu.au (B. Ujvari).

[1] BU, RAG and FT designed and wrote the manuscript, the authors contributed equally to the article.

http://dx.doi.org/10.1016/j.meegid.2016.02.005
1567-1348/

1. Introduction

Cancer development and progression represent an evolutionary and ecological process in which cells that acquire selective advantages via genetic and/or epigenetic modifications are able to proliferate autonomously, avoid immune recognition and undergo clonal expansion.

By infecting and colonizing another host (rather than dying with the host) and hence persisting in the population, transmissible cancers can occupy an empty niche not available to non-transmissible cancers. Here we investigate and discuss the key factors necessary for cancer cell transmission. We propose that similar to host–parasite interactions, successful transmission of cancer requires a 'perfect storm' with the confluence of multiple host (micro- and macro-environmental factors) and tumour cell traits.

2. Transmissible cancers in nature

Although many cancers are induced by infectious agents (Aktipis et al., 2015; de Martel et al., 2012; Ewald and Swain Ewald, 2015; Vittecoq et al., 2015, 2013), for a cancer to be truly transmissible, the cancer cell itself must move between hosts. So far only three transmissible cancers have been identified in the wild, but many more have been documented under experimental circumstances and in laboratory animals (Table 1, Box 1). In the current article we focus on transmissible cancers naturally occurring in the wild.

2.1. Canine transmissible venereal tumour (CTVT)

CTVT, is a globally distributed sexually transmitted tumour of canines (naturally occurring in dogs, experimentally transmitted to jackals and coyotes), that arose about 11,000 years ago in inbred dogs (Murchison et al., 2014; Murgia et al., 2006). CTVT has been proposed to have originated from a myeloid cell (reviewed in (Das and Das, 2000; Mukaratirwa and Gruys, 2003)) and is considered to be the oldest known somatic cell line (Murchison et al., 2014; Murgia et al., 2006; Strakova and Murchison, 2015). The neoplasms are located mainly on the external genitalia of dogs (Das and Das, 2000; Mukaratirwa and Gruys, 2003). The cancer cells are transmitted across the histocompatibility barriers during coitus (Belov, 2011). The extensive abrasions and bleeding of penile mucosa and vagina potentially facilitate the transmission of the malignant cells.

Experimental transplantation studies revealed three distinct life history phases of CTVT, described as progressive, stable and regressive stages (reviewed in Murchison (2008)).

The progressive phase generally lasts for a few weeks, followed by a stable phase lasting from weeks to months, resulting in an approximately 80–90% cell loss (Murchison, 2008). In experimental set ups, following the stable phase, CTVT cells either (i) enter a regressive phase lasting between 2 and 12 weeks and resulting in the disappearance of the tumours, or (ii) re-enter a progressive growth phase leading to metastasis (Murchison, 2008). In naturally occurring CTVT the progressive and stable phases have been documented in details, but only limited information describing spontaneous regression is available (reviewed in Murchison, 2008). Due to the various latencies of the different CTVT growth phases (lasting for weeks and months), and not all CTVT cells entering the different stages at the same time (e.g. 80–90% of CTVT cells enter the stable phase, the remaining 10–20% have the potential for transmission), there is a possibility for the tumour cells to be transmitted throughout the life of CTVTs.

2.2. Devil facial tumour diseases (DFTD)

DFTD was first observed in Tasmanian devils (*Sarcophilus harrisii*) in north-eastern Tasmania, Australia, in 1996 (Hawkins et al., 2006). The disease presents as large ulcerating tumours around the face and jaws of the devils. Since 1996 DFTD has spread across Tasmania and massively depleted devil numbers (McCallum et al., 2009). Similar to CTVT, transmission requires direct contact and DFTD is passed between devils by biting during social interactions (McCallum et al., 2009). DFTD frequently (70%) metastasizes to distant organs, and in most cases results in death within 6 to 9 months after the emergence of the first lesions (Pyecroft et al., 2007). In contrast to CTVT, DFTD does not enter a stable or regressive phase, and hence the host and the cancer have not reached a homeostatic stage, which would slow down the spread of DFTD.

Recently a second variant of DFTD (now described as DFTD2, and the previous lineage renamed as DFTD1) has been described in Tasmanian devils by Pye et al. (2015). The two devil cancers, DFT1 and DFT2 both cause phenotypically similar facial tumours, but with different underlying histological, karyotypic and genetic characteristics (Pye et al., 2015). The presence of remnants of X chromosomes in DFTD1, and a Y chromosomes in DFT2 further distinguishes the two aneuploid cancer lineages, and indicates that the former one has most likely arisen in a female, while the second one in a male devil (Murchison et al., 2012; Pye et al., 2015).

The emergence of DFTDs has been attributed to the extremely low level of genetic diversity of devils, with particularly reduced polymorphism at the non-self-recognising immune genes, the Major Histocompatibility Complex molecules (reviewed in Belov, 2012). Although the two lineages are carrying different MHC genotypes, they are both capable of colonizing MHC disparate hosts. Siddle et al. (2013b) proposed that DFT1 escapes T cells destruction by epigenetically downregulating MHC expression on the tumour cell surface. It is highly predictable that DFTD2 avoids immune recognition by following similar pathways, especially since the same mechanism is frequently employed by tumour cells in human malignancies (Fassati and Mitchison, 2010).

Whether epigenetic regulation facilitates the spread of DFTD2 remains to be answered. Nevertheless, the low genetic diversity of devils has most likely predisposed them to become ideal microenvironment for tumour development and evolution (as supported by the relatively high incidence of neoplasia in devils (Griner, 1979)).

2.3. Clam leukaemia (CL)

Although disseminated, haematopoietic or hemic neoplasia, have been described in many bivalves, it has only recently been shown that this malignant clonal cell line is horizontally transmitted in soft-shell clams (*Mya arenaria*) (Metzger et al., 2015). CL is characterized by abnormal amplification of cells in the haemolymph, diseased cells lose their phagocytic abilities, express a novel surface antigen, and display cytoplasmic sequestration of the *TP53* tumour suppressor protein (Walker et al., 2011). CL was first described in the 1970s, and is now distributed along the east coast of North America, causing the decimation of soft-shell clam populations (Metzger et al., 2015).

3. Transmissible cancers in evolutionary context

Cancer development and progression represent an evolutionary process as Darwinian selection drives cancer cells along evolutionary landscapes within a single host (Greaves and Maley, 2012). However, ultimately the malignant cells perish with the host so that every cancer must 're-invent' a successful strategy to overcome host defences.

Occasionally, rare events allow cancer cells to be transmitted from one host to another, leading to a special case of inter-individual metastasis. In the classical metastatic process, tumour cells adapted to the primary tissue site must evolve strategies to survive and proliferate in the 'foreign' environment of a distant and often quite different tissue (Box 1, 2) (Gatenby and Gillies, 2008). In contrast, in transmissible cancers, cancer cells typically grow in different hosts but in similar tissue. Here we examine the properties of both tumour cells and host organisms that permit transmission.

Table 1
Transmissible cancers occurring naturally in the wild and under experimental and incidental circumstances.

	Transmissible cancers occurring in the wild				Human cases			Laboratory animals		Natural transmission across the parasite–host-interface
	Canine venereal tumour disease (CTVT)	Devil facial tumour disease (DFTD1)	Devil facial tumour disease (DFTD2)	Clam leukaemia (CL)	Pregnancy	Organ transplantation	Experimental and incidental cases	Contagious reticulum cell sarcoma (CRCS)	Surgical, orthotopic implantation of human tumours into laboratory animals	Tapeworm cancer
Species affected	Dogs, wolves, coyotes and jackals	Tasmanian devil (*Sarcophilus harrisii*)	Tasmanian devil (*Sarcophilus harrisii*)	Soft-shell clams (*Mya arenaria*)	Human (*Homo sapiens*)	Human (*Homo sapiens*)	Human (*Homo sapiens*)	Syrian hamster (*Mesocricetus auratus*)	Mouse (*Mus musculus*)	Tapeworm (*Hymenolepis nana*) – Human (*Homo sapiens*)
Appeared	>10,000 years ago	>20 years ago	Five cases reported from 2014 and 2015	>40 years ago	Ongoing	Ongoing	Occasional	1960s	Ongoing	2013
Distribution	Worldwide	Tasmania	Tasmania	North Atlantic coast	Worldwide	Worldwide	Worldwide	Laboratory colony	Laboratory colonies	Colombia
Cell of origin	Myeloid cells	Schwann cells or precursors	Schwann cells or precursors	Haemocytes	Various	Various	Various	Neoplastic histiocytes	Human cancer cells	Stem cells
Permissive environment	Low genetic diversity of host species	Low genetic diversity of host species	Low genetic diversity of host species	Potential environmental stress	Immune privileged womb and placenta, and genetically related	Immune supressed recipient and immune matched donor	Genetically related (daughter to mother) and not known	Not known	Inhibited immune system	HIV patient immune-compromised
Spreads via	Sexual intercourse and licking of affected areas	Social interactions (mating and fighting for food)	Social interactions (mating and fighting for food)	Filtration of seawater contaminated with neoplastic cells	Haematogenous (blood) and/or lymphatic circulation across placenta	Physical transplantation of organs containing cancer cells (anthropogenic vector)	Physical transplantation of cancer cells (anthropogenic vector)	Implantation, feeding on the ulcerated tumours, direct contact, via vectors (mosquitoes)	Physical transplantation of cancer cells (anthropogenic vector)	Haematogenous (blood) and/or lymphatic circulation systems
Gender specificity	None	None	So far only males	None	Females to offspring	None	None	None	None	Male patient
Primary tumours	Genitalia	Face	Face	Haemolymph	Varies	Varies	Varies	Upper lip, subcutaneous	Varies	Tapeworm stem cells
Metastasis	Rare	70%	Not known	100% (invade all tissues)	Varies	Varies	Varies	100%	Varies	Lymph-nodes, lungs, liver and adrenal glands
Mortality	Rare	Close to 100%	Not known	Close to 100%	Varies	Varies	Varies	Animals were euthanized	Animals are euthanized	Patient died

Box 1
Transmissible cancers occurring under experimental circumstances, in laboratory animals and in the wild.

Human cases.

Pregnancy.

During pregnancy the placenta and the foetus are immune privileged, protected from immune rejection, therefore facilitating the transmission of malignant cells at the maternal-foetal interface and intrauterine (Dingli and Nowak, 2006; O'Neill, 2010; Warning et al., 2011). Although rare, mother-to-foetus as well as foetus-to-foetus cancer transmission have been reported (Dingli and Nowak, 2006; Tolar and Neglia, 2003; Welsh, 2011).

Organ transplantation.

Organ transplantation artificially creates an immunocompromised state, by matching the immune profile of the donor and the recipient, and by suppressing the immune system of the recipient to avoid organ rejection. Prior to strategic screening of donors for malignancies 30% of organ recipients developed donor-derived cancers (Gandhi and Strong, 2007; Penn, 1978), since 1997 the prevalence dropped to 0.05% (Engels et al., 2011).

Accidental transmission.

A few rare cases of accidentally and experimentally transmitted tumours have been reported (Welsh, 2011): including the transmission of cancer cells from a patient to a surgeon during operation (Gärtner et al., 1996), a needle-stick transfer to a laboratory technician (Gugel and Sanders, 1986), the experimental tumour transmission between a daughter and her mother, as well as to volunteers (Scanlon et al., 1965; Southam and Moore, 1958), and the injection of prisoners in the 1950's and 1960's with cancer cells (Loue, 2000).

Animal cases.

Syrian hamster — contagious reticulum cell sarcoma (CRCS).

A spontaneous reticulum-cell sarcoma of Syrian hamster (*Mesocricetus auratus*) arose in a laboratory colony in the 1960s (Brindley and Banfield, 1961). CRCS was transferred between animals, either by subcutaneous implantation, by feeding on the ulcerated tumours, by cage contact, or via mosquito bites (Banfield et al., 1965; Brindley and Banfield, 1961).

Canine transmissible venereal tumour (CTVT).

CTVT, is a globally distributed sexually transmitted tumour of canines, that arose about 11,000 years ago in inbreed dogs (Murchison et al., 2014; Murgia et al., 2006). CTVT generally appears within two months after transmission and rarely results in metastasis, and rarely kills the host animal (Das and Das, 2000; Mukaratirwa and Gruys, 2003).

Devil Facial Tumour Disease (DFTD).

DFTD1 of Tasmanian devils (*Sarcophilus harrisii*) was first observed in NE Tasmania, Australia, in 1996 (Hawkins et al., 2006). Recently a second variant, DFTD2, was described from 5 male devils from the South-East of Tasmania (Pye et al., 2015). DFTDs are passed between devils by biting during social interaction (McCallum et al., 2009). DFTD1 frequently (70%) metastasizes to distant organs, and in most cases kills the host animal (Pyecroft et al., 2007).

Clam leukaemia (CL).

A horizontally transmitted hemic neoplasia, abnormal amplification of cells in the haemolymph, was recently discovered in soft-shell clams (*M. arenaria*) (Metzger et al., 2015). CL was first observed in the 1970s, and it's currently distributed along the east coast of North America, causing the decimation of soft-shell clam populations (Metzger et al., 2015).

Laboratory animal models.

Surgical, orthotopic implantation of human tumours into mice (with inhibited immune system) has become a standard model for personalized medicine. The system mimics tumour cell stromal interactions and permits preclinical analysis of therapeutic compounds (Hoffman, 2015; Manzotti et al., 1993).

Natural transmission across the animal — human interface.

A unique case of abnormal malignant tapeworm cells (*Hymenolepis nana*) invading the lymph-nodes, lungs, liver and adrenal glands of an HIV patient has recently been reported by Muehlenbachs et al. (2015). The authors proposed that the patient's immunocompromised state has most likely facilitated the proliferation of *H. nana* stem cells which concomitantly has led to the accumulation of somatic mutations and malignant transformation. This unique cancer serves as clear example of infectious cancer recorded in an additional phylum, the Plathyhelminths.

4. The ecology and evolution of transmissible cancer development

A cancer cell's fitness is governed by its own proliferation. Thus, the underlying Darwinian dynamics will select for cell properties that maximize proliferation in local tissues. The fitness of infectious cancer cells is additionally defined by their ability to be transmitted from one host to another, suggesting that, as for other infectious agents, Darwinian forces will tend to maximize the transmission related traits. The spread of a transmissible cancer to a new host, similar to the metastatic cascade, is a complex, multi-step biological process, with distinct micro- and macro-environmental barriers (Gatenby and Gillies, 2008; Ujvari et al., 2015). The metastatic cascade involves the initiation and growth of cancer cells at primary tumour sites, followed by angiogenesis to feed the growing tumour and invasion of the stromal tissue surrounding the primary tissue (Nguyen et al., 2009). Once cells acquire the capacity to disassemble the extracellular matrix and enter the lymphatic or blood microvessels (intravasation), they have the opportunity to disseminate throughout the body of the host. Many circulating tumour cells survive the transit but die within the foreign metastatic site but, some survive by arresting in the capillary beds within distant organs and extravasate into the new host tissue (Hanahan and Weinberg, 2011; Nguyen et al., 2009). The future path of the invading cells, however remains uncertain. Most simply die in the foreign tissue over time, some form microscopic metastases and progress no further. A very small minority of metastatic cells ultimately colonize the new tissue site forming a clinically apparent tumour (Nguyen et al., 2009).

Although transmissible cancers follow a similar path, they face additional hurdles including transmission to a new host followed by, overcoming immunologic responses due to histocompatibility barriers (self/nonself recognition), adapting to negative environmental signals

Box 2
The key factors of successful transmission.

Several attributes of parasites/pathogens and hosts have been proposed to govern transmission success (here 'parasite' and 'pathogen' are used interchangeably).
Parasite characteristics include higher reproductive rate and shorter generation time than the host, virulence (Frank and Schmid-Hempel, 2008), shedding rates and infective dose (Barfield et al., 2015; Leggett et al., 2012), phenotypic plasticity (Reece et al., 2009), asexual and/or sexual reproduction and switching between the two (Barrett et al., 2008), and being able to function in a wide range of physical conditions, including survival outside the host (Walther and Ewald, 2004).
Transmission to other hosts can potentially present as an allocation trade-off: greater propagules emigrating from the infected host may result in reduced pathogen load and slower pathogen population growth in the original host (Barfield et al., 2015). However, when conditions become unsuitaible for further persistence in the infected host, pathogens that translocate to new hosts of the same species will aquire higher fitness (Frank and Schmid-Hempel, 2008). Increased within-host replication and concomitantly higher virulence and transmission rate utlimately result in the deceleration of transmission and virulence reaching evolutionary equilibrium (particularly in horizontally transmitted pathogens) (Bolker et al., 2010; Lipsitch and Moxon, 1997; Lipsitch et al., 1996).
The invasion of novel hosts, and hence parasite fitness, is also governed by the fraction of propagules leaving the host (per capita shedding rates) and by the number of cells required to successfully infect a host: infective dose (Leggett et al., 2012). Host demography and environmental stochasticity can hinder establishment success, therefore the number of propagules released, the number of introduction attempts and rate, and temporal and spatial patterns of propagule arrivals can influence the probability of a successful transmission (Engering et al., 2013; Leggett et al., 2012).
One of the fundamental questions of disease ecology is, how parasites adapt to the new host environment. Phenotypic plasticity (Louhi et al., 2013; Reece et al., 2009) and the ability to switch between different life history strategies (fast and slow, or also referred as r- and k- selected life histories (Reznick et al., 2002) at the dynamic stages of colonization (dissemination, translocation, survival between hosts and establishment in new host) have been proposed to be crucial for successful transmission (Andrews and Rouse, 1982; Barrett et al., 2008). Additionally invading pathogens suppress and/or evade host immune responses via the release of biochemical molecules, which then affects parasite survival within the host and confers higher fitness to the invasive pathogens (Frank and Schmid-Hempel, 2008; Schmid-Hempel, 2009; Sorci et al., 2013).
Naturally, hosts have evolved numerous mechanisms to detect, attack and hence reduce and/or prevent parasitic invasions (Gilchrist and Sasaki, 2002). Therefore, apart from pathogen traits, a permissive, susceptible host environment is a key element necessary for successful transmission (Leggett et al., 2012). Infection occurrence and intensity are generally more prominent in individuals in poor condition and the presence of susceptible hosts can result in rapid and widespread spread of the disease (Beldomenico and Begon, 2010).
Spatial and temporal heterogeneity in physical attributes of the within- and between host environments, including structural variables, resource availability and distribution (Cressler et al., 2014; Engering et al., 2013), as well as the potential of co-and super infections with other parasites (Syller, 2012), will determine whether the host can resist invasions, and if not, to what extent the colonization by a new pathogen will impact on the host species and the host population.
Rate and magnitude with which a pathogen can spread from host to host potentially across greater geographic distances can be significantly increased by being associated with vectors (Engering et al., 2013). Vectors can break down ecological, geographical barriers, transport and directly deposit invasive pathogens into novel permissive host environments, and influence propagule pressure as well as the speed and the range of infection (Engering et al., 2013).
By affecting the distribution, abundance and reproduction of host species, parasites can also influence the evolution of host organisms. The impact of parasites on host fitness: causing rapid host death ('killers'), directly attacking host reproductive organs ('castrators'), and/or reducing overall host fitness ('debilitators') will ultimately determine the rate and direction of host-pathogen coevolution (Barrett et al., 2008; Lafferty and Kuris, 2002). Pathogens evoking host mortality will contrive stronger selection on host resistance compared to those reducing fecundity. Evolutionary responses of host to selection from parasites include altered immune defences (Maizels, 2009), changes in distribution, resource and habitat use and adjustments of behaviour and life history strategies and traits (Poulin and Thomas, 1999; Lefèvre et al., 2009; Ohlberger et al., 2010).

including growth-restricting environments, deficiencies in essential nutrients, and finally promoting the necessary host response such as angiogenesis to permit colonization of the invasion site (Gatenby and Gillies, 2008). Similar to metastatic cancers, interruption of any of these steps due to non-permissive genetic mutations or environmental constraints can halt the transmission cascade (Gatenby and Gillies, 2008).

Thus, given the extremely low probability of success at each of these steps, it is not surprising that contagious cancers are exceedingly rare. Nevertheless, based on the investigations of transmissible cancers and by drawing on the analogy with host–parasite interactions (Box 2), it is possible to infer some properties that are necessary for cancer cells to spread to and grow in a new host. These include: 1. Permissive circumstances facilitating transmission of cancer cells to a new host. 2. Tumour tissue properties that permit shedding of large numbers of malignant cells 3. Tumour cell phenotypic plasticity that permits survival during transmission and growth in a new host. 4. A 'permissible' host or host tissue environment.

5. Permissive circumstances facilitating transmission of cancer cells to a new host

In contrast to metastatic cancers in which the haematogenous (blood) and/or lymphatic circulation systems act as vectors in the dissemination of invasive cells (Nguyen et al., 2009), the cells of contagious cancers must be transmitted between individuals with sufficient efficiency that they arrive in the new host fully capable of adapting and replicating. As true parasites, transmissible cancers can use either physical or environmental transport systems: (i) direct contact (DFTD, CTVT), (ii) environmental transport (CL), (iii) vectors (Contagious reticulum cell sarcoma (CRCS) of Syrian hamster), and/or the capacity of infective stages to remain alive outside the host (Box 2) (Walther and Ewald, 2004). For example, while DFTD and CTVT cells rely on physical contact for transmission, the spread of CL is driven by environmental factors. Although the exact transmission route of CL is not known, it has been suggested that, because clams are filter feeders, CL spreads via filtration of seawater contaminated with neoplastic cells

(Metzger et al., 2015). Since haemocytes from a leukemic clam can survive in seawater for >6 h, ocean currents can be significant environmental vectors facilitating CL colonization of novel areas (Metzger et al., 2015).

6. Tumour and cellular properties necessary for transmission

6.1. Infective dose — propagule pressure

Apart from vector availability (Ewald, 1983), the probability of a successful colonization of novel hosts also depends on the introduction effort which includes the number of individuals/cells shredded per introduction (Barfield et al., 2015), the number of introduction events and the infective dose necessary for successful establishment (Leggett et al., 2012). Since, both CTVT and DFTD are transmitted by sexual and/or other frequent social contacts, the potential for transmission is relatively high. In addition, to permit an adequate size of the propagule, the tumour must release a large numbers of cells with each contact (Barfield et al., 2015; Leggett et al., 2012). Similar dynamics appear to play a significant role within-host metastatic cancer in which the release of tens of thousands of cancer cells into the circulation is necessary to achieve a metastasis success rate of 0.01% (Chambers et al., 2002). In transmissible cancers, the necessary tumour inoculum can be estimated based on observations that 10^5 to 10^6 DFTD1 cells are necessary to form tumours in immunocompromised mice (Kreiss et al., 2011). Tumour cells grown in laboratory mice not only mimicked and maintained the transmissibility of DFTD, but also appeared to have acquired additional characteristics to speed up the invasion process (Kreiss et al., 2011). Repeated transmission episodes are also likely to increase the probability of success despite the potential for initiating an immune response. A DFTD vaccine trial revealed that a combination of dead cancer cells and adjuvant injected into devils only provided short term protection when the animals were re-challenged with additional, but different strains of DFTD1 (first Strain 2, followed by Strain 3, DFTD1 variants determined based on their karyotypes (Pearse et al., 2012)) (Kreiss et al., 2015).

Thus, it is likely that spatial and temporal variation in propagule pressure and introduction effort are significant driving force behind the spread of transmissible cancers. An explicit prediction from this analysis is that selection for 'infectious cancers' would likely promote primary tumours with reduced cell adherence to other tumour cells or to the underlying stroma to maximize shedding of cells. To the best of our knowledge, this has so far not been investigated.

6.2. Genetic and phenotypic plasticity

Similar to pathogens, phenotypic plasticity (generated by genetic and epigenetic modifications), is likely to be essential for efficient transmission and invasion of cancer cells (in both intra- and inter-individual transmissions) (Gatenby and Gillies, 2008; Rodenhiser, 2009). Allowing the invading cells to respond to developmental and environmental cues (Rodenhiser, 2009), the adaptive genome must orchestrate dynamic, adaptive and reversible phenotypic properties that ensure rapid transition between fast and slow life history strategies (reviewed in Aktipis et al., 2013). For example, cues of resource abundance can initiate a proliferative phenotype by facilitating expression of oncogenes via hypomethylation, and blocking tumour-suppressor genes by hypermethylating corresponding promoters. Once resources are scarce, by re-adjusting methylation states, a quiescent, dormant phenotype can be achieved (Aktipis et al., 2013). Hypermethylation of genes responsible for immune recognition (resulting in immune system evasion), or hypomethylation of genes involved in cell adhesion can potentially provide invasive cancer cells with evolutionary benefits at different stages of colonization, both within and between organisms (Aktipis et al., 2013; Hanahan and Weinberg, 2011). Although the involvement and (epigenetic) regulation of various proteins (e.g. cadherins and integrins) in tethering or inhibiting the metastatic cascade have been well characterised in metastatic cancers (Hanahan and Weinberg, 2011), their role has so far been overlooked in transmissible cancers.

Importantly, although DFTD1 cells are remarkably stable at the genetic and genomic level (Deakin et al., 2012; Grueber et al., 2015; Murchison et al., 2012), they show high methylomic plasticity, which has been proposed to provide enhanced adaptive potential to DFTD1 cells as they colonize new hosts (Ujvari et al., 2013) (Box 4).

Interestingly, DFTD1 cells have similar levels of methylation to peripheral nerve cells (Schwann cells, SCs), the tissue from which DFTD has originated (Murchison et al., 2010), both being hypermethylated compared to other tissues (Ujvari et al., 2013). Peripheral nerve cells, particularly myelinating SCs possess astonishing plasticity that can be manipulated via epigenetic regulations to reverse or change functional and developmental commitments (Masaki et al., 2013). Remarkably by hijacking the programming apparatus of adult

Box 3
Carcinogenesis as speciation events.

According to the speciation theory of cancer evolution, carcinogenesis, particularly the evolution of transmissible cancers, have been described as novel speciation events (Duesberg et al., 2011; Vincent, 2010). The theory postulates that carcinogenesis is initiated by loss or gain of chromosomes (aneuploidy), which results in destabilization of karyotypes followed by strong selection for reproductive autonomy – the primary characteristics of species and cancer cells. Reproductive autonomy will result in stabilization of aneuploid genomes and the development of relatively stable karyotypes (different from the one of their host), resulting in the evolution of novel organisms (Duesberg et al., 2011; Vincent, 2010). Since transmissible cancers have individual clonal karyotypes (highly stable but bearing the signatures of aneuploidy), are immortal, and remained stable in countless natural transmissions — manifesting the lifestyle of extrinsic infectious microorganisms — they have been proposed to be natural examples of 'immortal fully speciated cancers' (Duesberg et al., 2011; Vincent, 2010).

Are transmissible cancers common, we just fail to recognize them?

It is possible that during the aeons of evolution several contagious cancers could have evolved, but they have actually driven their hosts to extinctions. While extinction is only expected to occur with density-dependent disease transmission if the pathogen critically destabilizes or reduces the size of its host's population, there is no threshold density for parasite persistence in models that assume complete frequency-dependence (e.g. sexually and vector- transmitted diseases). Transmissible cancers therefore will be able to persist when host population density is too low to allow ordinary infectious diseases to prevail. Therefore deterministic transmissible cancer-driven host extinction is possible with frequency dependent transmission (McCallum et al., 2009; Ryder et al., 2007). Consequently, it is conceivable that contagious cancers might have been more frequent in the wild, but because our perception only spreads across a tiny snapshot of the evolutionary timescale, we fail to recognize extinct contagious cancers. For example CTVT has reached an evolutionary stale-mate with its host over the last 10,000 years, and hence will most likely survive, but since both DFTD and CL result in the death of the host, these transmissible cancers might go extinct with their hosts.

Box 4
Evolutionary changes promoting rapid evolution of transmissible cancers.

Stress-induced modification of the genome.
Exposure to novel biotic (e.g. pathogens and overcrowding) or abiotic (e.g. UV exposure) conditions can induce genomic instability and hence influence phenotypic plasticity and adaptive potential of invasive species and cells (Bond and Finnegan, 2007). The origins of CL has been linked to the activation of the retroelement *Streamer* (Arriagada et al., 2014), which might have been stimulated by environmental stressors, such as pollution, temperature and overcrowding (Arriagada et al., 2014; Barber, 2004). The activation of *Steamer* in *M. arenaria* bears the signatures of a catastrophic genomic instability, which could have contributed to the initiation and development of CL. Elevated *Steamer* copy numbers potentially drive further genomic instability and accelerate disease progression. CTVT also carries the marks of ultraviolet light exposure and retrotransposon insertions (Murchison et al., 2014), a long interspersed nuclear element (*LINE-1*) being inserted near the c-*myc* oncogene in the CTVT genome (Liao et al., 2003; Murgia et al., 2006).
Overcoming genomic decay.
The high metabolic rate and the absence of recombination of asexual clonal cells result in the irreversible accumulation of deleterious mutations in neoplastic cells. Increasing chromosome numbers (polyploidy) of malignant cell therefore is a potential adaptation to the asexual lifestyle of cancer cells: polyploids are being able to sustain a higher mutation rate, and provide an adaptive advantage to cancer cells by masking deleterious mutations and ameliorating genomic decay (Merlo et al., 2010; Otto, 2007; Ujvari et al., 2014). Conquering Muller's ratchet is particularly important for the survival of transmissible cancers that are passaged across infinite numbers of hosts. CTVT uses additional mechanisms to overcome the decay of its mitochondrial genome: CTVT periodically captures mtDNA from its host to rejuvenate its mitochondria and to rescue its mitochondrial function, and thus increases fitness (reviewed in (Rebbeck et al., 2009; Strakova and Murchison, 2015; Ujvari et al., 2015)). Elevated chromosome numbers have been observed in the oldest strain of DFTD1 (Strain 1, the karyotype variant identified from the first tumours studied (Pearse et al., 2012; Ujvari et al., 2014), in CL (Metzger et al., 2015) and in CRCS (Banfield et al., 1965). Larger karyotypes (e.g. tetraploids) can also increase the adaptive potential of transmissible cancers. The immediate consequence of polyploidization is a general rise in cell volume, and slower development due to increased genome size (Gregory, 2001; Otto, 2007; Ujvari et al., 2014). Therefore cells containing smaller karyotypes (e.g. diploid) will have the advantage of faster growth and higher proliferative potential and, hence will be selected for. However, larger karyotypes and slower growing cells can also have selectively advantage in certain circumstances, e.g. predation evasion. DFTD1 has been shown to rapidly respond to a novel selective regime by changing its ploidy, when selection favoured slower growing tumours, and hence avoid detection and removal together with the affected host (Ujvari et al., 2014).

SCs, *Mycobacterium leprae* has been shown to epigenetically reprogram them to a progenitor/stem-like stage and to render the infected cells highly proliferative, migratory and immunomodulatory (Masaki et al., 2013). Therefore, it is possible that the high epigenetic plasticity of the tissue of origin could have contributed to the emergence of DFTD1.

Apart from epigenetic factors, dynamic telomere homeostasis observed in DFTD1 could also potentially contribute to high phenotypic plasticity and provide this cancer with enhanced adaptive potential as it colonizes its novel hosts (Bender et al., 2014; Ujvari et al., 2012).

Additionally, to overcome the histocompatibility barrier upon transmission into a novel host, transmissible cancers in vertebrates (similar to primary and metastatic cancers in humans (Fassati and Mitchison, 2010)), appear to employ epigenetic immune modulation by down-regulating genes involved in the antigen-processing pathways resulting in the concomitant loss of cell surface expression of *MHC Class I*, and active evasion of immune recognition (Belov, 2011; Fassati and Mitchison, 2010; Siddle and Kaufman, 2013a, 2015; Siddle et al., 2013a)).

In CTVT during the progressive stage the immune system fails to control cancer growth due to proposed epigenetic down regulation of *MHC* expression on tumour cell surfaces. Although further evidence would be welcome, it has been suggested that, similar to human cancers (Fassati and Mitchison, 2010), shortly after cancer establishment and progression, cell surface *MHC* gene expression is being restored and significantly increases via the potential removal of epigenetic signals; and as a result, the immune system recognizes the malignant cells, and the tumour either stabilizes or regresses (Belov, 2011; Fassati and Mitchison, 2010; Siddle and Kaufman, 2013b).

Similar to CTVT, laboratory experiments found low or no *MHC class I* molecule expression on DFTD1 cell surfaces originating from tumour biopsies and from those kept in cell cultures (Siddle and Kaufman, 2013a, 2013b; Siddle et al., 2013a). Furthermore, in vivo experiments showed that *MHC* expression can be restored on DFTD1 cell surfaces by inhibiting the epigenetic regulator, histone deacetylase (Siddle and Kaufman, 2013a). Therefore, Siddle and Kaufman (2013b) proposed that DFTD1 might follow an evolutionary path similar to CTVT and evolve into less aggressive subtypes via regulating *MHC* cell surface expression and concomitant immune-modulation.

However, this does not appear relevant to CL transmissions since invertebrates do not possess *MHC* molecules. Although, they do employ other self/non-self recognition mechanisms to combat transformed malignant cells (Metzger et al., 2015; Voskoboynik et al., 2013) it is not yet known if these histocompatibility systems are genetically and/or epigenetically modulated in CL. The unique transmission of CL cells, surviving in natural seawater and proposedly transmitted via filtration (Metzger et al., 2015), certainly suggests a high degree of phenotypic plasticity and adaptability to both the hosts' micro- and macro-environment (Ujvari et al., 2015).

6.3. Tumour properties that promote cell transmission

Cancer cells habitually alter their micro-environment by creating novel niches less favourable to competitors and to reduce the risk of predation by the immune system (Alfarouk et al., 2013; Schmid-Hempel, 2009). Cancer cells frequently use aerobic glycolysis to produce energy (Gatenby and Gillies, 2004). The result of this unusual glycolysis is increased lactic acid production and the creation of a hypoxic and acidic microenvironment. The latter also support stromal remodelling, growth of blood vessels, and the escape of immune surveillance by recruiting immune-suppressor cells (Gabrilovich and Nagaraj, 2009). In addition, producing *ATP* at a higher rate but at lower yields also provides malignant cells with other selective advantages, including the inducement of oncogenes by lactate, the by-product of anaerobic glycolysis (Hans et al., 2009). As the acidic environment reduces the viability and function of normal cells, including immune cells, consequently the use of aerobic glycolysis might therefore be an adaptation to reduce both competition and predation with ultimately enhancing cancer cell fitness. Finally, the low extracellular pH of tumours also promotes invasiveness, migratory behaviour and facilitating metastasis (Gatenby et al., 2006; Hanahan and Weinberg, 2011). The strategies transmissible cancer cells use to alter their microenvironment upon transmission and to establish

themselves in the novel habitat have so far received little or no attention and remains to be an important question to be answered in order to understand the ecology and evolution of these unique cancers.

An important point to make, is that since non-transmissible cancer cells perish with the death of host, they have to reinvent the wheel, start from scratch and develop the malignant genotypes and phenotypes on the evolutionary landscape of genomes which have already adapted for their control (Haig, 2015). In contrast, by invading a new host, transmissible cancer cells manage to escape the anti-cancer mechanisms of the host and maintain their malignant genotypes and phenotypes across generations. These scenarios might explain why all naturally occurring transmissible cancers are relatively young on an evolutionary scale, and why transmissible cancers are rare. Genomes which have evolved anti-cancer mechanisms over the aeons of evolution against selfish malignant cells, are most likely in a lag face in responding to the emergence of the currently observed transmissible cancers. Similar to host–parasite interactions ("Red-Queen" dynamics) (Schmid-Hempel, 2011; van Valen, 1973) both hosts and contagious cancer cells have to change continuously to keep up with each other's adaptations. Most likely previous transmissible cancers have been eliminated by the hosts' genomes responding to the fitness reducing consequence of cancer cells, but the adaptation of current host genomes is trailing behind the appearance of novel contagious cancer lineages. It is a question of (evolutionary) time before the current cancers reach an equilibrium with their host (e.g. CTVT), become extinct or outrun their host (as it currently appears with DFTD which might be driving its host species to extinction) (Box 3).

7. Host properties necessary for growth of transmitted tumour cells

7.1. Susceptible hosts — permissive environment

Similar to host–parasite interactions (Beldomenico and Begon, 2010), cancer site invasibility primarily depends on the immune competence of the host and the immune status of the local tissue. Inflamed, infected, or injured tissues or hosts are typically more vulnerable to cancer cell growth and establishment (Coussens and Werb, 2002). Vertebrate histocompatibility barriers generally prevent cell transmission between individuals. Loss of genetic diversity at key immune genes such as the *MHC*, and the modulation of immune responses can, however, create an immune permissive myopic environment allowing successful allograft colonization (reviewed in Siddle and Kaufman, 2015 (Box 2)). Indeed, the appearance and the success of DFTD and CTVT cancers to invade >150,000 hosts have been attributed to low host *MHC* polymorphism (Belov, 2012). Although no evidence is currently available, it has been suggested that CL has emerged during a period of potential environmental stressors that most likely have caused a disturbed and immune-challenged environment (Metzger et al., 2015), facilitating the development of the invertebrate malignancy.

7.2. Fellow travellers

An interesting question in both metastatic and transmissible cancers is whether the clonally selected abnormal stromal cells ('fellow-travellers') (reviewed in Polyak et al., 2009), which provide an optimal niche for primary tumour cells, accompany the invasive malignant cells during the course of invasion of new organs and/or host organisms? Alternatively, will novel tumour accommodating stromal environments arise at each site of tumour metastasis and transmission sites (Ujvari et al., 2015)? In the case of transmissible cancers, with every transmission these malignant cell lineages have to overcome the challenges of the novel microenvironment and establish an accommodating niche, not only within the same organism, but also across individuals. The need for 'fellow-travellers' to co-adapt to the novel host might be a distinguishing factor between metastatic and transmissible cancers, and might provide an additional explanation for the rarity of transmissible cancers.

Clearly further studies are needed to answer whether transmissible cancer cells have evolved to be self-sufficient, continuing to grow and spread without the need of supporting stromal cells, or exploit the benefits of the optimal niche created by their 'fellow-travellers', or having to create a novel tumour-accommodating niche upon every transmission event (Ujvari et al., 2015) (Box 4).

7.3. Interactions between cancer lineages — helper cells

The recent discovery of a second transmissible cancer variant of DFTD (Pye et al., 2015) poses interesting questions: would the two different lineages be restricted to different local populations of Tasmanian devils, or would they co- and/or super-infect the same hosts? Although the temporal discovery of the two variants suggests that DFTD2 might have arisen from DFTD1, it is more likely that the two diseases arose separately (due to the significant difference in their karyotypes and genotypes), and could have potentially co-existed in the host population for some time. The fact that DFTD2 has so far been found only in males suggests that it might be a "specialist" in that it is optimized for transmission from male to male. DFT1 apparently can be passed between the genders and so in this context is a relative generalist. However, further studies are needed to establish whether the two variants are gender specific and are sympatric or allopatric, and whether they are capable of co-infecting the same host. Mixed infections of plant viruses generally result in either synergetic and/or antagonistic interactions between the viral partners (Syller, 2012). In antagonistic virus–virus interactions one virus benefits more and gains higher fitness from the presence of the other. Under synergistic conditions the presence of two or more viruses positively effects the replication of either or both of the co-infecting viruses. Additionally under the "helper-dependence" interaction one virus may support the transmission of its counterpart (Syller, 2012). Currently the interference interaction of DFTD1 and DFTD2 remains a question: would the presence of two variants lead to 'cross-protection' or 'mutual exclusion'? The experimental and theoretical framework applied in mixed plant virus infection research (Syller, 2012) could potentially provide a starting point to understand the epidemiology of DFTD infections.

8. Evolutionary adaptations to transmissible cancers

By affecting host fitness (via impeding reproduction and survival) parasites also influence the evolution of the host organisms (Barrett et al., 2008; Lafferty and Kuris, 2002). Apart from altered immune defences (Maizels, 2009), evolutionary responses of host to selection from parasites also involve the adjustments of behaviour and life history strategies (Poulin and Thomas, 1999; Lefèvre et al., 2009; Ohlberger et al., 2010).

Therefore, we predict that since both CTVT and DFTD have negative impact on host fitness, natural selection should favour individuals capable of recognizing and avoiding infectious conspecifics (Vittecoq et al., 2015). However, as both CTVT and DFTD are transmitted during sexual encounters, adaptive strategies such as avoidance behaviour would reduce transmission and thus not be retained in the population (Hamede et al., 2009). Similarly, both DFTD and CL can be transmitted during feeding (Metzger et al., 2015; Welsh, 2011) (co-feeding on carcasses can result in fights and transfer of tumour cells between devils (Hamede et al., 2008), and clams being filter feeders) so that contact is unavoidable in typical adaptive landscapes. Consistent with this, evolved tolerance to CTVT is upregulation of immune recognition mechanisms (reviewed in Belov, 2011; Fassati and Mitchison, 2010) rather than less aggressive social behaviour (Vittecoq et al., 2015). In contrast, similar changes of the immune system have not thus so far been observed in DFTD. But, it does appear that Tasmanian devils are adapting through changing the onset of sexual maturity and transitioning from a iteroparous (multiple reproductive events) to a semelparous (single breeding) reproduction (Jones et al., 2008).

9. Concluding remarks

In conclusion, biological invasion by malignant cell lines remains a rare event. Successful pathogen (including microparasitic cancer cells) transmission, being on a geographical or on organismal scale, is a multiplayer and multistage process which requires the species to succeed at all of steps in order to become a successful invader. The elusive nature of the invasion process arises from the necessity of the contemporaneous availability of resource rich permissive environments, vectors and release of propagules, in combination with the host species processing all the essential genotype (e.g. low *MHC* diversity), phenotype and life history strategies. Similarly, tumours are ecosystems, just on a microscale, containing both evolving cancer cell populations and multiple host components (Alfarouk et al., 2013). To become invasive, cancer cells first have to acquire a highly plastic, migratory and immunomodulatory phenotype (and potentially the support of clonally selected abnormal stromal cells). On rare occasions, depending on the availability of vectors (physical route of transmission) and permissive environments (low *MHC* diversity of the host, immune privileged and/or inflamed sites) tumours acquire the ability to be transmitted among individuals and become contagious. Although intra-individual and inter-individual metastasis are two ways allowing cancer cells to colonize different areas, slight differences exist between the two processes. One of the salient factors of contagious cancers, which also distinguishes them from metastatic cancers, is that once the cancer cells leave their original host, they become allografts. The vertebrate immune system is generally very efficient at detecting and rejecting allografts, based on polymorphic surface proteins, notably the Major Histocompatibility Complex. Indeed it has been proposed that histocompatibility could have evolved due to selective pressure to prevent neoplasia and contagious cancers (Murgia et al., 2006). So far no immune molecule with similar histocompatibility role as *MHC* in vertebrates has been identified in invertebrates, making it possible that transmissible cancers like CL are more widespread among invertebrates than previously suspected. Particularly aquatic filter feeders might be at higher risk as malignant cells may potentially be transported by currents. Additionally, species with low genetic diversity, such as cheetahs, or California sea lions, are potentially at risk of not only developing cancer at higher than expected frequencies (e.g. urogential cancer in the latter), but also for the cancer cells to become transmissible (Ujvari and Belov, 2011).

Acknowledgements

We thank Thomas Madsen for helpful discussion on the topic. We are grateful to Beth Moorefield for valuable and constructive comments on the manuscript. FT is supported by the ANR (Blanc project EVOCAN) and by the CNRS (INEE). The authors have no conflict of interest to declare.

References

Aktipis, C.A., Boddy, A.M., Gatenby, R.A., Brown, J.S., Maley, C.C., 2013. Life history trade-offs in cancer evolution. Nat. Rev. Cancer 13, 883–892.
Aktipis, C.A., Boddy, A.M., Jansen, G., Hibner, U., Hochberg, M.E., Maley, C.C., Wilkinson, G.S., 2015. Cancer across the tree of life: cooperation and cheating in multicellularity. Philos. Trans. R. Soc. B 370.
Alfarouk, K.O., Ibrahim, M.E., Gatenby, R.A., Brown, J.S., 2013. Riparian ecosystems in human cancers. Evol. Appl. 6, 46–53.
Andrews, J.H., Rouse, D.I., 1982. Plant pathogens and the theory of r- and k-selection. Am. Nat. 120, 283–296.
Arriagada, G., Metzger, M.J., Muttray, A.F., Sherry, J., Reinisch, C., Street, C., Lipkin, W.I., Goff, S.P., 2014. Activation of transcription and retrotransposition of a novel retroelement, steamer, in neoplastic hemocytes of the mollusk Mya arenaria. Proc. Natl. Acad. Sci. U. S. A. 111, 14175–14180.
Banfield, W.G., Woke, P.A., MacKay, C.M., Cooper, H.L., 1965. Mosquito transmission of a reticulum cell sarcoma of hamsters. Science 148, 1239–1240.
Barber, B.J., 2004. Neoplastic diseases of commercially important marine bivalves. Aquat. Living Resour. 17, 449–466.
Barfield, M., Orive, M.E., Holt, R.D., 2015. The role of pathogen shedding in linking within- and between-host pathogen dynamics. Math. Biosci. 270 (Part B), 249–262.
Barrett, L.G., Thrall, P.H., Burdon, J.J., Linde, C.C., 2008. Life history determines genetic structure and evolutionary potential of host–parasite interactions. Trends Ecol. Evol. 23, 678–685.
Beldomenico, P.M., Begon, M., 2010. Disease spread, susceptibility and infection intensity: vicious circles? Trends Ecol. Evol. 25, 21–27.
Belov, K., 2011. The role of the major histocompatibility complex in the spread of contagious cancers. Mamm. Genome 22, 83–90.
Belov, K., 2012. Contagious cancer: lessons from the devil and the dog. BioEssays 34, 285–292.
Bender, H.S., Marshall Graves, J.A., Deakin, J.E., 2014. Pathogenesis and molecular biology of a transmissible tumor in the Tasmanian devil. Annu. Rev. Anim. Biosci. 2, 165–187.
Bolker, B.M., Nanda, A., Shah, D., 2010. Transient virulence of emerging pathogens. J. R. Soc. Interface 7, 811–822.
Bond, D.M., Finnegan, E.J., 2007. Passing the message on: inheritance of epigenetic traits. Trends Plant Sci. 12, 211–216.
Brindley, D.C., Banfield, W.G., 1961. A Contagious tumor of the hamster. J. Natl. Cancer Inst. 26, 949–954 (NP941-942, 955–957).
Chambers, A.F., Groom, A.C., MacDonald, I.C., 2002. Metastasis: dissemination and growth of cancer cells in metastatic sites. Nat. Rev. Cancer 2, 563–572.
Coussens, L.M., Werb, Z., 2002. Inflammation and cancer. Nature 420, 860–867.
Cressler, C.E., Nelson, W.A., Day, T., McCauley, E., 2014. Disentangling the interaction among host resources, the immune system and pathogens. Ecol. Lett. 17, 284–293.
Das, U., Das, A., 2000. Review of canine transmissible venereal sarcoma. Vet. Res. Commun. 24, 545–556.
de Martel, C., Ferlay, J., Franceschi, S., Vignat, J., Bray, F., Forman, D., Plummer, M., 2012. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 13, 607–615.
Deakin, J.E., Bender, H.S., Pearse, A.-M., Rens, W., O'Brien, P.C.M., Ferguson-Smith, M.A., Cheng, Y., Morris, K., Taylor, R., Stuart, A., Belov, K., Amemiya, C.T., Murchison, E.P., Papenfuss, A.T., Marshall Graves, J.A., 2012. Genomic restructuring in the Tasmanian devil facial tumour: chromosome painting and gene mapping provide clues to evolution of a transmissible tumour. PLoS Genet. 8, e1002483.
Dingli, D., Nowak, M.A., 2006. Cancer biology: infectious tumour cells. Nature 443, 35–36.
Duesberg, P., Mandrioli, D., McCormack, A., Nicholson, J.M., 2011. Is carcinogenesis a form of speciation? Cell Cycle 10, 2100–2114.
Engels, E.A., Pfeiffer, R.M., Fraumeni, J.F., Kasiske, B.L., Israni, A.K., Snyder, J.J., Wolfe, R.A., Goodrich, N.P., Bayakly, A.R., Clarke, C.A., Copeland, G., Finch, J.L., Fleissner, M.L., Goodman, M.T., Kahn, A., Koch, L., Lynch, C.F., Madeleine, M.M., Pawlish, K., Rao, C., Williams, M.A., Castenson, D., Curry, M., Parsons, R., Fant, G., Lin, M., 2011. Spectrum of cancer risk among U.S. solid organ transplant recipients: the transplant cancer match study. JAMA 306, 1891–1901.
Engering, A., Hogerwerf, L., Slingenbergh, J., 2013. Pathogen–host–environment interplay and disease emergence. Emerg. Microbes Infect. 2, e5.
Ewald, P.W., 1983. Host–parasite relations, vectors, and the evolution of disease severity. Annu. Rev. Ecol. Syst. 14, 465–485.
Ewald, P.W., Swain Ewald, H.A., 2015. Infection and cancer in multicellular organisms. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 370.
Fassati, A., Mitchison, N.A., 2010. Testing the theory of immune selection in cancers that break the rules of transplantation. Cancer Immunol. Immunother. 59, 643–651.
Frank, S.A., Schmid-Hempel, P., 2008. Mechanisms of pathogenesis and the evolution of parasite virulence. J. Evol. Biol. 21, 396–404.
Gabrilovich, D.I., Nagaraj, S., 2009. Myeloid-derived-suppressor cells as regulators of the immune system. Nat. Rev. Immunol. 9, 162–174.
Gandhi, M., Strong, D.M., 2007. Donor derived malignancy following transplantation: a review. Cell Tissue Bank. 8, 267–286.
Gärtner, H.-V., Seidl, C., Luckenbach, C., Schumm, G., Seifried, E., Ritter, H., Bültmann, B., 1996. Genetic analysis of a sarcoma accidentally transplanted from a patient to a surgeon. N. Engl. J. Med. 335, 1494–1497.
Gatenby, R.A., Gillies, R.J., 2004. Why do cancers have high aerobic glycolysis? Nat. Rev. Cancer 4, 891–899.
Gatenby, R.A., Gillies, R.J., 2008. A microenvironmental model of carcinogenesis. Nat. Rev. Cancer 8, 56–61.
Gatenby, R.A., Gawlinski, E.T., Gmitro, A.F., Kaylor, B., Gillies, R.J., 2006. Acid-mediated tumor invasion: a multidisciplinary study. Cancer Res. 66, 5216–5223.
Gilchrist, M.A., Sasaki, A., 2002. Modeling host–parasite coevolution: a nested approach based on mechanistic models. J. Theor. Biol. 218, 289–308.
Greaves, M., Maley, C.C., 2012. Clonal evolution in cancer. Nature 481, 306–313.
Gregory, T.R., 2001. Coincidence, coevolution, or causation? DNA content, cell size, and the C-value enigma. Biol. Rev. Camb. Philos. Soc. 76, 65–101.
Griner, L.A., 1979. Neoplasms in Tasmanian devils (*Sarcophilus harrisii*). J. Natl. Cancer Inst. 62, 589–595.
Grueber, C.E., Peel, E., Gooley, R., Belov, K., 2015. Genomic insights into a contagious cancer in Tasmanian devils. Trends Genet. 31, 528–535.
Gugel, E.A., Sanders, M.E., 1986. Needle-stick transmission of human colonic adenocarcinoma. N. Engl. J. Med. 315, 1487.
Haig, D., 2015. Maternal–fetal conflict, genomic imprinting and mammalian vulnerabilities to cancer. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 370.
Hamede, R.K., McCallum, H., Jones, M., 2008. Seasonal, demographic and density-related patterns of contact between Tasmanian devils (*Sarcophilus harrisii*): Implications for transmission of devil facial tumour disease. Aust. Ecol. 33, 1442–9993.
Hamede, R.K., Bashford, J., McCallum, H., Jones, M., 2009. Contact networks in a wild Tasmanian devil (*Sarcophilus harrisii*) population: using social network analysis to reveal seasonal variability in social behaviour and its implications for transmission of devil facial tumour disease. Ecol. Lett. 12, 1147–1157.

Hanahan, D., Weinberg, Robert A., 2011. Hallmarks of cancer: the next generation. Cell 144, 646–674.
Hans, H.K., Taeho, K., Euiyong, K., Ji Kyoung, P., Seok-Ju, P., Hyun, J., Han Jip, K., 2009. The mitochondrial Warburg effect: a cancer enigma. IBC 1, 7.
Hawkins, C.E., Baars, C., Hesterman, H., Hocking, G.J., Jones, M.E., Lazenby, B., Mann, D., Mooney, N., Pemberton, D., Pyecroft, S., Restani, M., Wiersma, J., 2006. Emerging disease and population decline of an island endemic, the Tasmanian devil Sarcophilus harrisii. Biol. Conserv. 131, 307–324.
Hoffman, R.M., 2015. Patient-derived orthotopic xenografts: better mimic of metastasis than subcutaneous xenografts. Nat. Rev. Cancer 15, 451–452.
Jones, M.E., Cockburn, A., Hamede, R., Hawkins, C., Hesterman, H., Lachish, S., Mann, D., McCallum, H., Pemberton, D., 2008. Life-history change in disease-ravaged Tasmanian devil populations. Proc. Natl. Acad. Sci. U. S. A. 105, 10023–10027.
Kreiss, A., Brown, G.K., Tovar, C., Lyons, A.B., Woods, G.M., 2015. Evidence for induction of humoral and cytotoxic immune responses against devil facial tumor disease cells in Tasmanian devils (*Sarcophilus harrisii*) immunized with killed cell preparations. Vaccine.
Kreiss, A., Tovar, C., Obendorf, D.L., Dun, K., Woods, G.M., 2011. A murine xenograft model for a transmissible cancer in tasmanian devils. Vet. Pathol. 48, 475–481.
Lafferty, K.D., Kuris, A.M., 2002. Trophic strategies, animal diversity and body size. Trends Ecol. Evol. 17, 507–513.
Lefèvre, T., Lebarbenchon, C., Gauthier-Clerc, M., Missé, D., Poulin, R., Thomas, F., 2009. The ecological significance of manipulative parasites. Trends Ecol. Evol. 24, 41–48.
Leggett, H.C., Cornwallis, C.K., West, S.A., 2012. Mechanisms of pathogenesis, infective dose and virulence in human parasites. PLoS Pathog. 8, e1002512.
Liao, K.-W., Lin, Z.-Y., Pao, H.-N., Kam, S.-Y., Wang, F.-I., Chu, R.-M., 2003. Identification of canine transmissible venereal tumor cells using in situ polymerase chain reaction and the stable sequence of the long interspersed nuclear element. J. Vet. Diagn. Investig. 15, 399–406.
Lipsitch, M., Moxon, E.R., 1997. Virulence and transmissibility of pathogens: what is the relationship? Trends Microbiol. 5, 31–37.
Lipsitch, M., Siller, S., Nowak, M.A., 1996. The evolution of virulence in pathogens with vertical and horizontal transmission. Evolution 50, 1729–1741.
Loue, S., 2000. Textbook of Research Ethics: Theory and Practice Springer Science & Business Media.
Louhi, K.-R., Karvonen, A., Rellstab, C., Jokela, J., 2013. Genotypic and phenotypic variation in transmission traits of a complex life cycle parasite. Ecol. Evol. 3, 2116–2127.
Maizels, R.M., 2009. Parasite immunomodulation and polymorphisms of the immune system. J. Biol. 8, 62.
Manzotti, C., Audisio, R.A., Pratesi, G., 1993. Importance of orthotopic implantation for human tumors as model systems: relevance to metastasis and invasion. Clin. Exp. Metastasis 11, 5–14.
Masaki, T., Qu, J., Cholewa-Waclaw, J., Burr, K., Raaum, R., Rambukkana, A., 2013. Reprogramming adult Schwann cells to stem cell-like cells by leprosy bacilli promotes dissemination of infection. Cell 152, 51–67.
McCallum, H., Jones, M., Hawkins, C., Hamede, R., Lachish, S., Sinn, D.L., Beeton, N., Lazenby, B., 2009. Transmission dynamics of Tasmanian devil facial tumor disease may lead to disease-induced extinction. Ecology 90, 3379–3392.
Merlo, L.M.F., Wang, L.-s., Pepper, J.W., Rabinovitch, P.S., Maley, C.C., 2010. In: Poon, R.Y.C. (Ed.), Polyploidy, aneuploidy and the evolution of cancer, polyploidization and cancer. Springer, New York, pp. 1–13.
Metzger, M.J., Reinisch, C., Sherry, J., Goff, S.P., 2015. Horizontal transmission of clonal cancer cells causes leukemia in soft-shell clams. Cell 161, 255–263.
Muehlenbachs, A., Bhatnagar, J., Agudelo, C.A., Hidron, A., Eberhard, M.L., Mathison, B.A., Frace, M.A., Ito, A., Metcalfe, M.G., Rollin, D.C., Visvesvara, G.S., Pham, C.D., Jones, T.L., Greer, P.W., Vélez, H.A., Olson, P.D., Diazgranados, L.R., Zaki, S.R., 2015. Malignant transformation of *Hymenolepis* nana in a human host. N. Engl. J. Med. 373, 1845–1852.
Murchison, E.P., 2008. Clonally transmissible cancers in dogs and Tasmanian devils. Oncogene. 27, S19–S30.
Mukaratirwa, S., Gruys, E., 2003. Canine transmissible venereal tumour: cytogenetic origin, immunophenotype, and immunobiology. A review. Vet. Q. 25, 101–111.
Murchison, E.P., Schulz-Trieglaff, O.B., Ning, Z., Alexandrov, L.B., Bauer, M.J., Fu, B., Hims, M., Ding, Z., Ivakhno, S., Stewart, C., Ng, B.L., Wong, W., Aken, B., White, S., Alsop, A., Becq, J., Bignell, G.R., Cheetham, R.K., Cheng, W., Connor, T.R., Cox, A.J., Feng, Z.-P., Gu, Y., Grocock, R.J., Harris, S.R., Khrebtukova, I., Kingsbury, Z., Kowarsky, M., Kreiss, A., Luo, S., Marshall, J., McBride, D.J., Murray, L., Pearse, A.-M., Raine, K., Rasolonjatovo, I., Shaw, R., Tedder, P., Tregidgo, C., Vilella, A.J., Wedge, D.C., Woods, G.M., Gormley, N., Humphray, S., Schroth, G., Smith, G., Hall, K., Searle, S.M.J., Carter, N.P., Papenfuss, A.T., Futreal, P.A., Campbell, P.J., Yang, F., Bentley, D.R., Evers, D.J., Stratton, M.R., 2012. Genome sequencing and analysis of the Tasmanian devil and its transmissible cancer. Cell 148, 780–791.
Murchison, E.P., Tovar, C., Hsu, A., Bender, H.S., Kheradpour, P., Rebbeck, C.A., Obendorf, D., Conlan, C., Bahlo, M., Blizzard, C.A., Pyecroft, S., Kreiss, A., Kellis, M., Stark, A., Harkins, T.T., Graves, J.A.M., Woods, G.M., Hannon, G.J., Papenfuss, A.T., 2010. The Tasmanian devil transcriptome reveals schwann cell origins of a clonally transmissible cancer. Science 327, 84–87.
Murchison, E.P., Wedge, D.C., Alexandrov, L.B., Fu, B., Martincorena, I., Ning, Z., Tubio, J.M.C., Werner, E.I., Allen, J., De Nardi, A.B., Donelan, E.M., Marino, G., Fassati, A., Campbell, P.J., Yang, F., Burt, A., Weiss, R.A., Stratton, M.R., 2014. Transmissible dog cancer genome reveals the origin and history of an ancient cell lineage. Science 343, 437–440.
Murgia, C., Pritchard, J.K., Kim, S.Y., Fassati, A., Weiss, R.A., 2006. Clonal origin and evolution of a transmissible cancer. Cell 126, 477–487.
Nguyen, D.X., Bos, P.D., Massagué, J., 2009. Metastasis: from dissemination to organ-specific colonization. Nat. Rev. Cancer 9, 274–284.
Ohlberger, J., Langangen, Ø., Edeline, E., Olsen, E.M., Winfield, I.J., Fletcher, J.M., James, J.B., Stenseth, N.C., Vøllestad, L.A., 2010. Pathogen-induced rapid evolution in a vertebrate life-history trait. Proc. R. Soc. Lond. B Biol. Sci. 278, 35–41.
O'Neill, I.D., 2010. Tasmanian devil facial tumor disease: insights into reduced tumor surveillance from an unusual malignancy. Int. J. Cancer 127, 1637–1642.
Otto, S.P., 2007. The evolutionary consequences of polyploidy. Cell 131, 452–462.
Pearse, A.-M., Swift, K., Hodson, P., Hua, B., McCallum, H., Pyecroft, S., Taylor, R., Eldridge, M.D.B., Belov, K., 2012. Evolution in a transmissible cancer: a study of the chromosomal changes in devil facial tumor (DFT) as it spreads through the wild Tasmanian devil population. Cancer Genet. 205, 101–112.
Penn, I., 1978. Tumors arising in organ transplant recipients. Adv. Cancer Res. 28, 31–61.
Polyak, K., Haviv, I., Campbell, I.G., 2009. Co-evolution of tumor cells and their microenvironment. Trends Genet. 25, 30–38.
Poulin, R., Thomas, F., 1999. Phenotypic Variability Induced by Parasites: extent and Evolutionary Implications. Parasitol. Today 15, 28–32.
Pye, R.J., Pemberton, D., Tovar, C., Tubioc, J.M.C., Dund, K.A., Fox, S., Darbya, J., Hayes, D., Knowles, G.W., Kreiss, A., Siddle, H.V.T., Swift, K., Lyons, A.B., Murchison, E.P., Woodsa, G.M., 2015. A second transmissible cancer in Tasmanian devils. Proc. Natl. Acad. Sci. 28, 2015. http://dx.doi.org/10.1073/pnas.1519691113 (published ahead of print December).
Pyecroft, S.B., Pearse, A.M., Loh, R., Swift, K., Belov, K., Fox, N., Noonan, E., Hayes, D., Hyatt, A., Wang, L., Boyle, D., Church, J., Middleton, D., Moore, R., 2007. Towards a case definition for devil facial tumour disease: what is it? EcoHealth 4, 346–351.
Rebbeck, C.A., Thomas, R., Breen, M., Leroi, A.M., Burt, A., 2009. Origins and evolution of a transmissible cancer. Evolution 63, 2340–2349.
Reece, S.E., Ramiro, R.S., Nussey, D.H., 2009. Plastic parasites: sophisticated strategies for survival and reproduction? Evol. Appl. 2, 11–23.
Reznick, D., Bryant, M.J., Bashey, F., 2002. R- and k-selection revisited: the role of population regulation in life-history evolution. Ecology 83, 1509–1520.
Rodenhiser, D., 2009. Epigenetic contributions to cancer metastasis. Clin. Exp. Metastasis 26, 5–18.
Ryder, J.J., Miller, M.R., White, A., Knell, R.J., Boots, M., 2007. Host–parasite population dynamics under combined frequency- and density-dependent transmission. Oikos 116, 2017–2026.
Scanlon, E.F., Hawkins, R.A., Fox, W.W., Smith, W.S., 1965. Fatal homotransplanted melanoma. A case report. Cancer 18, 782–789.
Schmid-Hempel, P., 2009. Immune defence, parasite evasion strategies and their relevance for 'macroscopic phenomena' such as virulence. Philos. Trans. R. Soc. Lond. B Biol. Sci. 364, 85–98.
Schmid-Hempel, P., 2011. Evolutionary Parasitology: The Integrated Study of Infections, Immunology, Ecology, and Genetics. Oxford University Press, NY.
Siddle, H.V., Kaufman, J., 2013a. How the devil facial tumor disease escapes host immune responses. OncoImmunology 2, e25235.
Siddle, H.V., Kaufman, J., 2013b. A tale of two tumours: comparison of the immune escape strategies of contagious cancers. Mol. Immunol. 55, 190–193.
Siddle, H.V., Kaufman, J., 2015. Immunology of naturally transmissible tumours. Immunology 144, 11–20.
Siddle, H.V., Kreiss, A., Tovar, C., Yuen, C.K., Cheng, Y., Belov, K., Swift, K., Pearse, A.-M., Hamede, R., Jones, M.E., Skjødt, K., Woods, G.M., Kaufman, J., 2013a. Reversible epigenetic down-regulation of MHC molecules by devil facial tumour disease illustrates immune escape by a contagious cancer. Proc. Natl. Acad. Sci.
Siddle, H.V., Kreiss, A., Tovar, C., Yuen, C.K., Cheng, Y., Belov, K., Swift, K., Pearse, A.-M., Hamede, R., Jones, M.E., Skjødt, K., Woods, G.M., Kaufman, J., 2013b. Reversible epigenetic down-regulation of MHC molecules by devil facial tumour disease illustrates immune escape by a contagious cancer. Proc. Natl. Acad. Sci. 110, 5103–5108.
Sorci, G., Cornet, S., Faivre, B., 2013. Immune evasion, immunopathology and the regulation of the immune system. Pathogens 2, 71–91.
Southam, C.M., Moore, A.E., 1958. Induced immunity to cancer cell homografts in man. Ann. N. Y. Acad. Sci. 73, 635–653.
Strakova, A., Murchison, E.P., 2015. The cancer which survived: insights from the genome of an 11,000 year-old cancer. Curr. Opin. Genet. Dev. 30, 49–55.
Syller, J., 2012. Facilitative and antagonistic interactions between plant viruses in mixed infections. Mol. Plant Pathol. 13, 204–216.
Tolar, J., Neglia, J.P., 2003. Transplacental and other routes of cancer transmission between individuals. J. Pediatr. Hematol. Oncol. 25, 430–434.
Ujvari, B., Belov, K., 2011. Major histocompatibility complex (MHC) markers in conservation biology. Int. J. Mol. Sci. 12, 5168–5186.
Ujvari, B., Papenfuss, A.T., Belov, K., 2015. Transmissible cancers in an evolutionary context. Inside Cell 1, 1–10.
Ujvari, B., Pearse, A.-M., Peck, S., Harmsen, C., Taylor, R., Pyecroft, S., Madsen, T., Papenfuss, A.T., Belov, K., 2013. Evolution of a contagious cancer: epigenetic variation in devil facial tumour disease. Proc. R. Soc. B Biol. Sci. 280.
Ujvari, B., Pearse, A.-M., Swift, K., Hodson, P., Hua, B., Pyecroft, S., Taylor, R., Hamede, R., Jones, M., Belov, K., Madsen, T., 2014. Anthropogenic selection enhances cancer evolution in Tasmanian devil tumours. Evol. Appl. 7, 260–265.
Ujvari, B., Pearse, A.-M., Taylor, R., Pyecroft, S., Flanagan, C., Gombert, S., Papenfuss, A.T., Madsen, T., Belov, K., 2012. Telomere dynamics and homeostasis in a transmissible cancer. PLoS One 7, e44085.
van Valen, L., 1973. A new evolutionary law. Evol. Theory 1, 1–30.
Vincent, M.D., 2010. The animal within: carcinogenesis and the clonal evolution of cancer cells are speciation events sensu stricto. Evolution 64, 1173–1183.
Vittecoq, M., Ducasse, H., Arnal, A., Møller, A.P., Ujvari, B., Jacqueline, C.B., Tissot, T., Missé, D., Bernex, F., Pirot, N., Lemberger, K., Abadie, J., Labrut, S., Bonhomme, F., Renaud, F., Roche, B., Thomas, F., 2015. Animal behaviour and cancer. Anim. Behav. 101, 19–26.

Vittecoq, M., Roche, B., Daoust, S.P., Ducasse, H., Missé, D., Abadie, J., Labrut, S., Renaud, F., Gauthier-Clerc, M., Thomas, F., 2013. Cancer: a missing link in ecosystem functioning? Trends Ecol. Evol. 28, 628–635.

Voskoboynik, A., Newman, A.M., Corey, D.M., Sahoo, D., Pushkarev, D., Neff, N.F., Passarelli, B., Koh, W., Ishizuka, K.J., Palmeri, K.J., Dimov, I.K., Keasar, C., Fan, H.C., Mantalas, G.L., Sinha, R., Penland, L., Quake, S.R., Weissman, I.L., 2013. Identification of a colonial chordate histocompatibility gene. Science 341, 384–387.

Walker, C.W., Van Beneden, R.J., Muttray, A.F., Böttger, S.A., Kelley, M.L., Tucker, A.E., Thomas, W.K., 2011. Chapter one - p53 superfamily proteins in marine bivalve cancer and stress biology. In: Michael, L. (Ed.), Advances in Marine Biology. Academic Press, pp. 1–36.

Walther, B.A., Ewald, P.W., 2004. Pathogen survival in the external environment and the evolution of virulence. Biol. Rev. Camb. Philos. Soc. 79, 849–869.

Warning, J.C., McCracken, S.A., Morris, J.M., 2011. A balancing act: mechanisms by which the fetus avoids rejection by the maternal immune system. Reproduction 141, 715–724.

Welsh, J.S., 2011. Contagious cancer. Oncologist 16, 1–4.