Abstract
In recent years, immune systems have sparked considerable interest within the philosophy of science. One issue that has received increased attention is whether other phyla besides vertebrates display an adaptive immune system. Particularly the discovery of CRISPR-Cas9-based systems has triggered a discussion about how to classify adaptive immune systems. One question that has not been addressed yet is the transgenerational aspect of the CRISPR-Cas9-based response. If immunity is acquired and inherited, how to distinguish evolutionary from immunological adaptation? To shed light on this issue and obtain conceptual clarity, I will investigate the inheritance of small RNA responses to pathogens in the nematode *C. elegans* as a further potential instantiation of a transgenerational adaptive immune system. I will explore how to make sense of systems that lie at the crossroads between genetic, immunological, and evolutionary spheres and explore the consequences of a transgenerational perspective on immune systems for immunology and its philosophy.

Keywords Philosophy of immunology · Adaptive immune systems · Epigenetics · Small RNA inheritance · Immune memory

Introduction
The philosophy of immunology is one of the most pulsating fields within the philosophy of biology (Swiatczak 2014; Tauber 2017; Pradeu 2020). Recent advances include work on theories of immunogenicity, tumor biology, symbiosis, and biological individuality (Pradeu 2006, 2016; Rondeau et al. 2019; Chiu and Gilbert 2015). Immunological processes have been proposed as among the primary determinants of individuality. For instance, insisting on a separation of the evolutionary and the physiological individual, Pradeu (2016) argues that the way the immune system
negotiates and demarcates the organism and the environment should be considered one of the best candidates for processes that define the individual within one generation (reviewed in Suárez and Stencel 2020).

As is the case for the life sciences in general, immunology and its philosophy are heavily influenced by the types of model organisms they study (Ankeny and Leonelli 2020). In the case of immunology, jawed vertebrates’ immune systems are central. Other instantiations of immune systems, such as invertebrate, bacterial, or plant immune systems, are often described in terms of "lack of." They are described and understood in terms of what properties they miss compared to jawed vertebrate immune systems (e.g., Jones and Dangl 2006; Engelmann and Pujol 2010). One cornerstone of vertebrate immunology that invertebrates and plants have traditionally been thought to "lack" is adaptive immunity, that is, immunological processes that, after launching a response to a particular trigger, guarantee upon second exposure a faster and stronger response to that same trigger. This conjecture is primarily based on these organisms "lacking" cell-based immune responses akin to the clonal expansion and selection of B- and T-lymphocytes (Klein 1989).

In the last few decades, there has been a lively debate about many instances of invertebrates displaying some sort of memory to previous stimuli (reviewed in Milutinović and Kurtz 2016). It has, however, been argued that while "immune memory"—an umbrella term for all types of immune phenomena where there is some memory-based response to a second trigger (Pradeu and du Pasquier 2018), that is, where the second response is by some qualitative or quantitative measure different to the first response—is a fairly common phenomenon, "true" adaptive immunity might still be reserved for jawed vertebrates (Hauton and Smith 2007). What, exactly, sets apart adaptive immunity and immune memory is, however, still open for debate and it remains an important task to find ways to describe and differentiate kinds of adaptive immunity.

The development of B-cell-like and T-cell-like lymphocyte lineages in jawless vertebrates has solidified the idea that there are other instantiations of adaptive immune systems given that the somatic diversification of structurally distinct antigen receptor genes evolved independently in jawless and jawed vertebrates (Kaattari 1994; Alder et al. 2005; Herrin and Cooper 2010; Boehm 2011; Boehm et al. 2018). Furthermore, several other instantiations of adaptive-like processes have been described in invertebrates. In snails, fibrinogen-related proteins (FREPs) are highly diversified at a genomic level and can undergo somatic recombination (Zhang et al. 2004; Kurtz 2005; Melillo et al. 2018). In insects and crustaceans, alternative splicing of the Down Syndrome Cell Adhesion molecule (Dscam) can produce diversified, long-lasting immune responses (Watson et al. 2005; Armitage et al. 2015; Melillo et al. 2018). Furthermore, the inheritance of (adaptive-like) immune responses has been reported in invertebrate species (Little et al. 2005; Barribeau et al. 2016; Melillo et al. 2018; Rimer et al. 2014), introducing an aspect of (adaptive) immune responses usually not regarded characteristic of immunity in general. However, the transmission of antibodies through breast milk is a relatively well-established fact in mammals (Saderharju et al. 2007), suggesting that at least inter-generational persistence of immunity also occurs in jawed vertebrates. In addition, debates regards potential intergenerational inheritance of "trained" immunity in
mice have currently sparked debate (Katzmarski et al. 2021; Katzmarski et al. 2022; Kaufmann et al. 2022), making the issue of how to exactly conceptualize the inheritance of immune responses also relevant for the paradigm jawed vertebrate example.

Besides these findings in eukaryotes, the CRISPR-Cas9 system in bacteria and archaea (Ishino et al. 1987; Barrangou et al. 2007) has also been discussed for its qualification as an (adaptive) immune system (Pradeu and Moreau 2019; Koonin 2019; Veigl 2019). Regarding the CRISPR-Cas9-based system as an instantiation of an adaptive immune system poses, however, at least two interconnected challenges for the conceptualization of adaptive immune systems: First, CRISPR-Cas9-based immunity persists transgenerationally. Second, CRISPR-Cas9-based immune effectors are inherited genetically (as a part of DNA sequence), making it unclear whether to consider them as adaptive in an immunological or an evolutionary sense.

Questions about the inheritance of immune responses thus seem to be a promising new area to explore conceptual issues both in immunology and its philosophy. How to operationalize or classify adaptive immune systems if inheritance seems an important aspect? How would key concepts, such as the physiological individual, change if immunity extends beyond one generation? What are new areas of contact for the philosophy of immunology and the philosophy of epigenetics, given that heritable immune responses might be understood as the inheritance of acquired traits? What is immunologically and what is evolutionarily adaptive? In essence, a re-examination of the boundaries and fluidity between the immunological and the evolutionary is required.

In this article, I aim at commencing such a re-examination by introducing a further candidate for a transgenerational immune system—small RNA responses in the nematode *C. elegans*. Given that heritable small RNA responses ensure immunity transgenerationally but are being inherited in parallel to DNA, I will use the example to confront how to deal with systems that sit in between the immunological and the genetic/evolutionary. First, I will survey the recent discussion on what defines immune memory and carve out how to conceptually grasp what makes adaptive immunity special. Second, based on the elaborated classification, I will examine the case of small RNA inheritance in the nematode *C. elegans* and qualify it as an adaptive immune system. Finally, I will examine the bearing of the small RNA-based example on how to draw the line between the evolutionary and the immunological and discuss consequences both for the philosophy of immunology and scientific practice.

**Towards a classification of adaptive immunity**

To examine the adaptive character of immune responses, it will first be necessary to develop a characterization of adaptive immunity that captures the aspects that set adaptive immunity apart from other immune phenomena. In a recent article, Pradeu & du Pasquier argue for the multiple realizability of immune memory, cf: "We propose immunological memory is "multiply realizable," which means that it can be achieved through extremely different mechanisms. Immunological memory is a gradual and multidimensional phenomenon, and therefore cannot be captured by any
dichotomy” (Pradeu & du Pasquier 2018, 8). They propose that immune memory functions locate on a spectrum and can be described and differentiated by the extent they realize five different characteristics of immune memory:

1. “Strength: this dimension measures the degree of increase in strength (both quantitative and qualitative) of the second immune response upon rechallenge, in comparison with the first immune response.
2. Duration: this dimension measures how long the capacity for a stronger response upon rechallenge lasts.
3. Speed: this dimension represents the degree of increase in rapidity of the second immune response upon rechallenge, in comparison with the first immune response.
4. Specificity: this dimension shows whether the second response upon rechallenge is specific to a given target (e.g., a given pathogen), or on the contrary has a wide spectrum.
5. Extinction: this dimension illustrates whether the stronger response upon rechallenge is due to the mere persistence of a unique, prolonged, immune response, or rather to true reactivation, that is, a first immune response followed by an extinction of the response, and then by a new activation.” (Pradeu and Du Pasquier 2018, 14).

While Pradeu and Du Pasquier affirm that immune memory functions exist in a broad spectrum of phyla, (true) “adaptive immunity” is reserved for very few instantiations. Amongst all instantiations of immune systems they consider, they picture B- and T-lymphocytes as the only effectors that realize the five characteristics to a great extent (see Fig. 1) (they do, however, mention that jawless vertebrate immune memory might realize the characteristics in about the same way).

How to arrive from a characterization of immune memory at one of adaptive immunity? Given that adaptive immunity provides immune memory, any adaptive immune system will have to realize the characteristics discussed by Pradeu and du Pasquier (2018). These are, however, not sufficient to pinpoint what makes adaptive immunity special. Building on the characterization provided by Pradeu and du Pasquier (2018), textbook definitions of adaptive immunity (Abbas et al. 2012), as well as recent accounts reviewing the characteristics of potential instantiations of adaptive immune systems (Rimer et al. 2014), I propose the following characterization of adaptive immune systems, which is an attempt to capture a consensus about adaptive immune systems that developed influenced by the paradigm example of adaptive immunity in jawed vertebrates, but extending it for features which potential alternative instantiations of adaptive immune systems have brought to the forefront:

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1 It has recently been argued that the term “acquired” immunity might be more fitting than “adaptive” immunity, based on whether effectors are encoded in genetic material or somatically generated (Rimer et al. 2014). For the purpose of this article, I shall stick with the more common terminology, while having incorporated the thrust of the terminological clarification in the criterion introduced as “antigen recognition.” Thus, adaptive immunity is defined as those responses that address antigen diversity through somatic diversification processes.
1. **Antigen recognition**: A process needs to be in place that allows immune effectors to recognize (or cognize, depending on the cognitive metaphor in use (Tauber 2013)) a high diversity of potential antigens. Immune effectors, for instance, can diversify in either a "customized" (where the immune effector repertoire is present before the first trigger) or "tailor-made" (where complementary immune effectors are synthesized after exposure to a trigger) manner (Rimer et al. 2014);  
2. **Amplifiability**: The dimension to what extent antigen-specific immune effectors are amplifiable;  
3. **Extinction**: The second response has to be a true reactivation of the immune response;  
4. **Specificity**: The second response upon rechallenge has to be specific to a given target;  
5. **Immunizability (a) speed**: The second response upon rechallenge has to be faster.  
   (b) **strength** The second response upon rechallenge has to be stronger  
6. **Duration (within an individual)**: The dimension to what extent the capacity for a stronger response upon rechallenge lasts within one (physiological) individual;  
7. **Inheritance**: How long immunity lasts in a lineage of individuals, giving rise to three options.  
   (a) **intragenerational**: immunity is not heritable;  
   (b) **intergenerational**: immunity is heritable for as long as there has been direct material overlap between the biological entity in the lineage exposed to the trigger and the biological entities consecutively displaying immunity (F3 for those individuals within a species that are physically connected with offspring after
fertilization and F2 for individuals that are not) (Rechavi and Lev 2017; Perez and Lehner 2019);

(c) transgenerational: inheritance of immunity extends beyond the presence of material overlap between the biological entity in the lineage exposed to the trigger and the biological entities consecutively displaying immunity;

First of all, I shall consider B- and T-cell-based immunity in jawed-vertebrates and VLR-based immunity in non-jawed vertebrates, given the proposed functional equivalence between both immune responses. By functional equivalence, I denote that while each realizer differs biochemically and by its genetic encoding, the individual realizers fulfill the same or very similar tasks in the system. Thus defined, functional equivalence is one way to attain multiple realization. However, it is not the only way since one does not require all realizers in different systems to be functionally equivalent to produce the same surface phenomenon (adaptive immunity).

How vertebrate immune systems realize most criteria has already been discussed in Pradeu and du Pasquier (2018). I need to add that antigens are recognized in a "customized" way—that is, the receptor repertoire predates the first trigger. Somatic hypermutation can, however, further diversify and fine-tune the repertoire during proliferation (Weigert et al. 1970; Bernard et al. 1978). Memory duration within an individual spans a substantial part of the organism’s lifetime. Inheritance is confined to one generation (maternal transfer of antibodies, in the jawed vertebrate case), and both display clonal amplification of effectors after triggers, even though in the VLR system, it is yet not clear whether clonal amplification and diversification are limited (Herrin and Cooper 2010; Boehm et al. 2018) (see Table 1).

Next, I shall probe FREP-based immunity in mollusks. Fibrinogen-related proteins are immunoglobulin superfamily domain-containing molecules induced after infection (Adema et al. 1997). They are highly diversified at a genomic level and are believed to undergo some form of somatic recombination (Kurtz 2005). FREPs bind to highly polymorphic proteins on parasite surfaces. This process has been shown to be specific and causes stronger and faster second responses (Portela et al 2013). Evidence on FREP-based immune memory duration is sporadic,
with one report documenting ten-day resistance in a snail with a 15–18 month life expectancy (Pinaud et al. 2016). FREP-based immunity has so far only been observed intra-generationally. How and whether FREPs are amplified after infection is yet unknown, and it is also unknown whether the receptor repertoire predates the infection (Milutinović and Kurtz 2016). Rimer et al. (2014), however, classify FREPs as "customized" with regards to antigen recognition. There are currently no indications regarding the "extinction" of the immune response. Given that FREPs, however, could be regarded as "memory molecules," their persistence together with a downregulation of the overall immune response would count as an instance of extinction (see Table 1).

Another example of potential adaptive immunity beyond vertebrates that has recently received much attention is Down Syndrome Cell Adhesion Molecules (Dscams) in insects and crustaceans, which are somatically diversified through alternative splicing producing over 10,000 isoforms in various species. They can thus function as pathogen recognition receptors on circulating hemocytes (Dong et al. 2006). Also, pathogen-challenged individuals have been shown to have a different splice variant repertoire than naïve ones (Dong et al. 2006). Experiments have suggested antigen specificity. Dscam-based resistance varies with model species but has been reported for several days (e.g., in honey-bees that live for about 20 weeks) and "chronic" (in king prawns that live for about 2–3 years) (Armitage et al. 2017). There are also reports of maternally transferred resistance, but not directly linked to Dscams (Milutinović and Kurtz 2016). A definitive test for a role of Dscam in immune memory is, however, still lacking (Armitage et al. 2017). While Dscams can realize specificity, immunizability has only been shown qualitatively (individuals are immunized) but not quantitatively (whether the responses are stronger and faster) (see, e.g. Chiang et al. 2013). Also, "extinction" has not been assessed yet, but given that Dscams could also be regarded as "memory molecules," their persistence after the downregulation of the general immune response could guarantee extinction. Similar to FREPs, how Dscams are amplified after infection is yet unknown, and it is also unknown whether the receptor repertoire predates the infection. However, Rimer et al. have also classified them as "customized" immune effectors (2014) (see Table 1).

Let us finally consider CRISPR-Cas9 as a potential realization of an adaptive immune system. CRISPR-Cas9-based immunity operates by incorporating fragments of phages ("spacers") into the host’s DNA (Nunez et al. 2014). These fragments will, upon repeated infection, help guide particular nucleases towards phage DNA. The nucleases subsequently destroy the genetic information of the intruder (Datsenko et al. 2012). Immunization is conferred, realized as a long-lasting capacity to respond stronger and faster to a particular trigger after the initial response is extinguished. Thus, CRISPR-Cas9 based immunity fulfills specificity, immunizability, extinction, and memory duration. The CRISPR-Cas9-based resistance lasts throughout an individual’s lifespan and further continues transgenerationally. The transcription of complementary spacers guarantees amplifiability after reinfection. However, whereas antigen recognition of all examples discussed so far was "customized," the CRISPR-Cas9 response
is tailor-made. In addition, the CRISPR-Cas9-based immune system displays an extremely high duration of memory since they last transgenerationally (see Table 1).

Conversely, Pradeu & du Pasquier indicate the duration of CRISPR-Cas9 based immunity to be somewhat lower than vertebrate immune systems, a surprising attestation given that acquired spacers persist in the host genome through the individual bacterial or archaeal cell’s life cycle as well as transgenerationally. They justify this choice because the duration is judged at the population and not the individual’s level (2018, 13). In a sense, the duration is somewhat disciplinarily situated in genetics, and thus they do not consider it directly importable onto immunological discourse. However, I do not see any straightforward reason for not considering the duration of CRISPR-Cas9 in an individual. From the time a particular element is acquired, we are justified to suspect that it remains incorporated as a genetic sequence until the subsequent cell division. This suspicion is grounded on knowing basic molecular biology about prokaryote replication and the stability of genetic elements within one generation. Thus, if we focus on acquired adaptive immunity in one generation, CRISPR-Cas9 based immune systems realize the duration to a great extent; i.e., after being acquired, they are very likely to persist until the next progenation event.

How CRISPR-Cas9 based systems acquire information about a particular trigger links immune- and genetic systems. The acquisition of the capacity to specifically respond to a particular trigger is guaranteed by acquiring a particular genetic element. As a result, adaptive immunity is heritable. Traditionally, all heritable components of the immune system are considered "innate," adaptive immunity is believed to be of a non-germline character. Is CRISPR-Cas9 based immunity thus beyond the grasp of any concept of adaptive immunity? How should we conceptualize immune phenomena that last beyond one generation? In the next section, I will explore another case of transgenerationally maintained immune responses that transmit acquired information: small RNA inheritance. I will use this case study to determine how and where to draw the line between genetically and/or immunologically adaptive systems.

A closer look into the transgenerationality of adaptive immune systems

In this section, I will introduce small RNA responses in the invertebrate C. elegans as an instantiation of an (adaptive) immune system. Furthermore, I will discuss the transgenerational persistence of small RNA responses and consider the importance of considering not only innate but also some instances of adaptive immunity to extend the realms of one physiological individual. This section has two parts. First, I will introduce some intricacies of small RNA biology. Second, I will argue why small RNA responses should be considered instantiations of adaptive immune systems. Third, I will review arguments why the term "adaptive immunity" should be confined to vertebrate instantiations and argue why I think it is justified to understand the small RNA-based system as an instantiation of adaptive immunity.
Some notes on small RNA biology and inheritance in *C. elegans*

Quite generally, small RNAs are non-coding RNAs studied for their regulatory roles in almost all known species. Studies on small RNA-related effects were picked up in the 1980s and 1990s and culminated in identifying the phenomenon of "RNA interference" (Fire et al. 1998), referring to the fact that small RNAs interfere with, that is, change, gene expression (Veigl 2021). Small RNAs’ primary mode of action is the complementary binding of target RNAs, although mismatches are sometimes tolerated depending on the particular class of small RNAs (Saxena et al. 2003). To ensure this targeting, small RNAs often rely on other effector proteins.

Small RNAs are best known for targeting and sometimes destroying complementary messenger RNAs, inhibiting the synthesis of a specific protein. Small RNAs are involved in several regulatory tasks, such as defense against selfish genetic elements (Malone and Hannon 2009), metabolic regulation (Cai et al. 2009), and defense against viruses (Hamilton and Baulcombe 1999). Several different small RNA species are defined based on different biochemical properties. Across model organisms, however, tasks of particular species of small RNAs vary. Thus it is essential to point out before going into the details of small RNA responses in a particular model organism that these are no general claims and cannot be extrapolated easily onto other model species or even transformed into general sentences.

In almost all organisms that display small RNA-based gene regulatory circuits, small RNAs have been implicated as important regulators of stress responses to biotic and abiotic triggers. In plant and invertebrate immunology, they are believed to be critical effectors of what is generally perceived as the "innate" immune system (McManus 2004). In these scenarios, small RNAs, together with other immune effectors, guarantee resistance to these triggers by implementing gene regulatory changes that fine-tune the organism’s physiology towards a specific resistance to the particular trigger (Wilkins et al., 2005; Gammon 2017). While there is a small RNA-arm of the jawed vertebrate immune system, it is generally treated as neglectable, for it operates much slower than cell-based immune responses (Cullen and Cherry 2013).

As described above, small RNA’s primary mechanism of action is complementary binding. Let me thus discuss the best-established example for small RNA-based immune responses: the anti-viral response. Upon viral infection, viral dsRNA intermediates trigger the production of virus-derived small interfering RNAs (viRNAs) that guarantee virus-dependent immunity by guiding effector molecules to viral RNAs, leading to the viral RNAs’ destruction. viRNAs-guaranteed viral immunity was coined an "acquired trait." Given that viRNAs persist after infection and are believed to immunize *C. elegans* against further exposures, they could also be considered an instantiation of immune memory (Rechavi et al. 2011; Sterken et al. 2014; Gammon et al. 2017).

Small RNA-based immunity against viruses can be considered immune memory in two separate ways: First, viRNAs are believed to instantiate immunity against repeated infection in the same generation. However, *C. elegans* has a short generation time of 3–5 days. Thus, second, viRNAs have been shown to persist transgenerationally and guarantee resistance against viruses in the offspring of worms exposed...
to the virus (Rechavi et al. 2011; Sterken et al. 2014; Gammon et al. 2017). Significantly, in reported cases, not only the resistance to future exposures was documented, but also the persistence of viRNAs, suggesting a solid causal link between the persistence of the complementarity-based cause and its effect, anti-viral resistance. Recently, another instantiation of small RNA-based transgenerational resistance to another pathogen, *Pseudomonas aeruginosa*, has been documented. In this case, the resistance is realized by acquiring and amplifying a small regulatory RNA of bacterial origin (Kaletsky et al. 2020). This small RNA leads to *P. aeruginosa* avoidance behavior in subsequent generations.

In the small RNA inheritance discourse, transgenerational anti-viral resistance is most of the time framed as an "acquired trait," "Non-mendelian inheritance," "Lamarckian inheritance," or "evolutionary adaption" (e.g., Rechavi et al. 2011; Rechavi and Lev 2017). Thus, the discourse is shaped by a focus on genetics. It is, however, equally possible to look at the persistence of anti-viral RNAs from the perspective of adaptive immunity. Small RNA-based responses realize specific immunity against a particular stimulus over an amount of time that is not confined to one physiological individual but persists transgenerationally. Small RNAs could thus be regarded as instantiating a particular type of immunity: adaptive, transgenerational immunity. In the following section, I will assess and defend this claim.

**Introducing transgenerational, adaptive immunity (TAI)**

In this section, it will be my goal to defend my claim that small RNA-based transgenerational resistance to environmental triggers, such as virus infection, instantiates transgenerational adaptive immunity (TAI). While there is, of course, contend in the scientific literature on the particularities of small RNA inheritance, whether it is evolutionary relevant, or whether the data gathered are too artificial, I take the transgenerationality as sufficiently established for this paper out of two reasons: (1) This paper does not concern the "how long?" question. Reports on small RNA-based effects in the parental—F3 generation are sufficient to call the inheritance phenomena transgenerational. Whether small RNA-based traits might also be relevant on evolutionary timescales is not the focus of this paper. (2) While there are discussions about certain particularities, I consider the basic phenomenology sufficiently well-established by several reports published by independent laboratories. In addition, the small RNA inheritance community seems to agree that while some details might not be figured out/well-defined, the phenomenological description is accurate.

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Here, it will be the most important task to establish whether small RNAs are adaptive in an immunological sense. Pradeu argues that "there is immunity when..."
there is a receptor capable of interacting with an antigenic pattern, even if this antigenic pattern is repeated in nature” (2011, 21). If a receptor is everything that recognizes structures, functions, or both, then it is possible to maintain this definition. Pradeu & Du Pasquier (2018) do not explicitly discuss C. elegans small RNA responses, but they discuss the systemic spreading and persistence of anti-viral small RNAs in Drosophila melanogaster (Saleh et al. 2009). In this vein, they argue that this small RNA-based system displays parallels with mammal adaptive immunity (2018, 11). It will now be of essence to explore these parallels further and assess how small RNAs realize the criteria for adaptive immunity introduced in “Towards a classification of adaptive immunity” section (see Table 1).

**Antigen recognition**

The diversity of small RNA immune receptors is grounded in a "tailor-made" immune response. Small RNAs are manufactured after a pathogen has entered the organism, using genetic information of the pathogen as a blueprint. Thus, the receptor repertoire does not predate the infection.

**Amplifiability**

Small RNAs are both receptors and immune effectors. Small RNAs are amplifiable through RNA-dependent RNA Polymerases (RdRPs). Amplification occurs at high rates after first and second triggers, while steady-state RdRP-based amplificatory circles ensure maintenance. RdRPs are not excessively mistake-prone, so amplified small RNAs are expected to be of the same nucleotide sequence as was the template they were amplified from (i.e., a process akin to "somatic hypermutation" has not been described yet).

**Extinction**

Small RNA-based immunity is only one partition of the nematode’s immune response. In analogy to memory B and T lymphocytes, which persist after the infection is cleared, complementary small RNAs, such as viRNAs, persist after the infection is cleared. Still, they do not actively execute immune effector functions without a second trigger.

**Specificity**

For the viral infection of C. elegans, it seems obvious how the response is specific—it is realized through sequence complementarity. Would small RNA-based resistance also have other unspecific effects? Quite likely. Changes in small RNA pools cannot be isolated to a single causally relevant small RNA if the concentration of one particular species of small RNAs increases, and given that effector molecules are limited sources, the concentration of other small RNAs might lead to other secondary effects (Sarkies et al. 2013). However, this does not change the fact that there are sequence-specific effects in the first place.
Immunizability (Speed & Strength)

While the notion of strength is ambiguous and touches both upon the quantitative and the qualitative, there are nevertheless two indications that suggest that the strength of the immune response after reexposure increases: (1) The maximum viral load during the second exposure is significantly lower than the maximum viral load of the first, suggesting a stronger response (Sterken et al. 2014); in addition, these findings point towards the persisting small RNAs responding faster than the first time, so the maximal viral load is decreased (= viral replication circles are stopped faster). In addition, the fact that anti-viral small RNAs do not have to be synthesized de novo but just amplified also suggests increased speed after the second exposure. (2) The recent literature suggests that "second triggers" boost small RNA-based gene silencing (Houri Ze’evi et al. 2016).

Memory duration

Small RNA-based anti-viral immunity guarantees the capacity to respond to a particular trigger for a substantial amount of time. Small RNA-based effectors persist throughout the worm’s life expectancy (3–5 days) after exposure to a virus.

Inheritance

Existing data suggest that small RNAs ensure resistance transgenerationally (Rechavi et al. 2011; Sterken et al. 2014; Gammon et al. 2017).

Based on the above elaboration, it seems justified to consider small RNA-based immunity as an instantiation of an adaptive immune system. The transgenerational aspect of the immune response is particularly interesting since it is not maintained by a change in genetic material but through the persistence of small RNAs, encoding information while at the same time being materially realized immune effectors. Therefore, small RNAs present an excellent case to think about the distinction of what to consider an immunological and what to consider a genetic adaptation. I shall examine the consequences of a transgenerational perspective on immune systems, probing situations at the crossroads of the genetic and the immunological. Before doing so, I shall address potential concerns when considering small RNA inheritance as an adaptive immune system.

How liberal should we be about adaptive immunity?

In the last section, I have suggested regarding small RNA-based resistance to biotic triggers as an instantiation of an adaptive immune system. While a growing amount of literature is pleading for a more liberal perspective on adaptive immune systems, several authors also make a case for confining adaptive immunity to vertebrates. Before dealing with the transgenerationality of immune
Adaptive immunity or evolutionary adaptation?…

systems, I shall examine arguments provided by critics and outline why I still think that viewing small RNA-based immunity as an adaptive immune system is a valuable perspective.

One standard line of critque is methodological, criticizing current research for being too much guided by looking for mechanistic analogies rather than starting from the phenomena (Little et al. 2005). Other critics are, however, wary of "whole organism" observations that lack mechanistic details and mainly rely on readouts such as survival or reproductive capacity. This line of critique demands clear, unambiguous, and reproducible evidence of specificity, memory, and extinction, a mechanistic underpinning, and extensive experimental testing (Hauton and Smith 2007; Melillo et al. 2018). In addition, critics plead for greater care when discussing which phenomena can be assessed at the level of the entire organism or the level of the cell (Melillo et al. 2018) and demand caution when importing vertebrate terminology onto observed phenomena (Hauton and Smith 2007).

Critics have dissuaded searches for vertebrate homologies (e.g., B-cell, T-cell, and MHC-like entities) in invertebrates (Klein 1989; Little et al. 2005), coining this endeavor the "homology trap" (Klein 1997). Authors thus warn to view invertebrate adaptive immunity-like phenomena as "ancestral" to vertebrate immune phenomena (Klein 1989). Another critical issue is the "specificity gap"—that host–pathogen specificity cannot be explained by the host’s genetic makeup (Little et al. 2005). Thus, specificity-generating mechanisms need to be demonstrated.

Other arguments go as far as denying complexity to invertebrate organisms, considering them incapable of producing large receptor repertoires, as well as denying that they can afford to set aside enough cells (and cell types) (Klein 1989, 1997). Such critics also argue that genetic rather than immunological adaptiveness makes more sense because of the short generation time of most invertebrates (Klein 1989). Another argument is that as genes coding for immune effectors and regulators occupy about 1% of the total jawed vertebrate genome, "smaller" genomes cannot afford that kind of space (Klein 1997).

To justify discussing the small RNA-based system as a "true" instantiation of an adaptive immune system, it is thus necessary to address these concerns. Broadly speaking, they can be separated into methodological and epistemological concerns. Methods first. Small RNA-based immune phenomena have not been discovered in the disciplinary context of immunology but rather in a (plant and C. elegans) genetics context. Therefore their discovery was likely not guided by a search for homologous mechanisms. This being said, Andy Fire and Craig Mello, the researchers who won the Nobel Prize for the discovery of RNA interference, referenced what was known in the 1990s about how the vertebrate immune system can register nucleic acids as an inspiration for their experimental setup (Fire et al. 1998). I believe that no strand of research can be free of presuppositions; that is, it cannot be free of the "bias of the known." However, for small RNA-based mechanisms, a relatively well-established mechanistic underpinning has been demonstrated, and the criteria of specificity, extinction, and memory have been reported. Also, small RNAs research addresses the "specificity gap" through a reasonably well understood "tailor-made" mechanism of antigen recognition.
Epistemology second. Why use the same terminology for systems that are so different? There are two parts to this question. One concerns adaptive immunity within one generation. The other concern is whether transgenerationality makes the system a subject for genetics or evolutionary biology, not immunology. Here I shall deal with the first issue. The second issue will be addressed in the next section. If we agree on the characteristics of adaptive immune systems I have provided in section two, then we should admit systems that realize certain aspects of adaptive immunity differently than do vertebrate immune systems. There can be multiple realizations of adaptive immunity as long as the proposed criteria are fulfilled. For instance, "tailor-made" antigen recognition is a mode of realizing this parameter that was only uncovered by investigating invertebrate instantiations of immune systems. Addressing antigenic diversity without a gene-by-gene approach seems to sit at the core of our ideas about adaptive immune systems. Thus, as long as we abstain from inferring homology but rather spell out the mechanistic details of the different realizations of antigen recognition, or any other characteristic of adaptive immunity, there should be no epistemic problems when considering small RNA-based immune systems as adaptive immune systems.

Before closing this section, I believe that one particular aspect of Klein’s criticism deserves special attention, which is the idea that genetic/evolutionary adaptation rather than immunological adaptation makes more sense for organisms with short lifecycles (Klein 1989). This line of thinking is related to considering the duration of CRISPR-Cas9 immunity on the population and not on the individual level (Pradeu and du Pasquier 2018), also suggesting the application of a thought style associated with (population) genetics onto the subject matter. CRISPR-Cas9 was discovered in a molecular genetics context and thus genetic terminology seems to stick, a phenomenon that might be similar for the small RNA case, which also has been established in genetics and biochemistry laboratories. At the same time, powerful metaphors, such as calling "customized" antigen recognition "Darwinian" and "tailor-made" antigen recognition "Lamarckian" are in use (Müller et al. 2018). Thus, there seems to be a sense of overlap or similarities between the modes of genetic and immune systems while at the same time a boundary between both phenomena seems to be (re)produced when considering alternative instantiations of immune systems. A closer examination of this boundary will be the task of the following section.

A transgenerational perspective on immune systems

Next, I shall deal with the issue of transgenerationality, particularly for small RNA- and CRISPR-Cas9-based immunity. There are important differences between B and T lymphocyte and small RNA/CRISPR-Cas9 based immune systems related to their effectors’ material structures. For instance, for small RNA- and CRISPR-based systems, the RNA-phase carries out the main effector functions, whereas, in B and T lymphocytes, it is the protein phase. On the other hand, while CRISPR-Cas and B and T lymphocyte effectors are encoded in DNA, small RNA-based immunity against viruses persists in an RNA form, meaning it does not have a phase of DNA-dependent RNA polymerase-mediated transcription, but
rather, RNA-dependent RNA polymerases amplify small RNAs. Other differences lie in the way both systems anticipate antigens ("customized" vs. "tailor-made") and the duration of the memory (inter- vs. transgenerational).

A particular aspect about transgenerational immune systems questions their belonging with adaptive immune systems. If we, e.g., consider the first generation after, say, a particular small RNA response to a virus was acquired, we might be tempted to consider the anti-viral small RNAs in the F1 generation as "innate." Whereas the parental generation has acquired the anti-viral RNAs, the respective RNAs in the F1 generation are "inherited," congenital, i.e., innate. The same goes for the example of CRISPR-Cas9-based systems. Whereas the parental generation acquired a particular spacer, the offspring genetically inherits the spacer, and thus, that particular spacer could be considered part of the innate immune response.

These questions are precisely where it becomes challenging to manage an instance where the boundaries of genetics and immunology overlap. Here, I will defend the claim that not all immune effectors that are inherited are innate. First of all, we can look at other instances of persisting immune effectors. Take maternal antibodies persisting in the newborn as an example; these effectors of the jawed vertebrate adaptive immune response are not considered innate immune effectors by persisting intergenerationally (Sadaharju et al. 2007). Second, persisting small RNAs are acquired and adaptive. Innate immune effectors will only change through the process of natural selection. This is not the case for persisting small RNAs—they change in a directed way caused by environmental conditions. Thus, they operate on different timescales and depend on other processes than traditional innate effectors.

Third, small RNA-based responses also do not persist indefinitely, as required for innate immune effectors changes. A change in the innate immune system would need to manifest genetically, that is, by mutation and is thus irreversible. Small RNA-based responses, however, are believed to persist for about 3–5 generations. The case of CRISPR-Cas9-based systems comes in salient here. Given that new spacers are genetically incorporated, they might be expected to persist indefinitely and thus "become" innate. On the one hand, similar to small RNA-based responses, they differ from innate immune effectors by the directedness of the acquisition, in their case, the directedness in the change of genetic material. On the other hand, it has been shown that spacers are being "lost" over time within an array of spacers (Martynov et al. 2017). Thus, their persistence is also shorter than genetically encoded innate immune effectors.

Nevertheless, the CRISPR-Cas9 system presents a challenging case since bacteria and phages do not possess a separated germline, and what exactly is (still) an immunological adaptation and what is (already) a genetic adaptation becomes hard to determine. Small RNA-based immune systems might thus be an even more straightforward example of an adaptive immune system, given that they are materially separated from the genome (particularly if they were synthesized from viral or bacterial genetic material). There is, however, an ongoing debate whether small RNA inheritance could be evolutionary relevant, either if small RNA-based responses could be maintained indefinitely (Devanpally et al. 2021) or whether there exists a mode of channeling small RNA responses into genetic change (via histone modifications,
making certain genetic regions more or less mutation prone (Makova and Hardison 2015)).

Lastly, and particularly for the case of small RNAs, it is important to differentiate what persists. Persisting small RNAs should not be understood as primarily coding immune effectors or immune effector functions, similar to how a particular stretch of DNA might code particular innate immune effectors. Instead, small RNAs are materially realized immune effectors. They realize their immune effector functions by their biochemical properties (i.e., a particular nucleotide sequence). Summing up, several reasons make it at least unintuitive to consider all inherited immune effectors innate immune effectors.

Clarificatory work is still to be done, however, regarding the difference between genetic and immunological adaptiveness. While a distinction between intra-, inter-, and transgenerational differentiates scales of inheritance, it is also necessary to investigate how the persistence of immunity is guaranteed. There are three possibilities: persistence is guaranteed genetically (through transmission of DNA), epigenetically (through the persistence of DNA regulatory patterns), or through the persistence of effectors. The transmission of maternal antibodies would be a case of intergenerational persistence through the persistence of effectors. CRISPR-Cas9 would be a case of genetically ensured transgenerational persistence.

Again, the small RNA case is interesting here since it is transgenerational but operates through the persistence of an immune effector. At the same time, small RNAs engage in epigenetic mechanisms ensuring their amplification and (Lev et al. 2017), in addition, as RNAs are information-bearing, amplifiable, and relatively stable, it would also check the box of genetic transmission. While these multiple roles seem to complicate the case at first glance, they set apart small RNAs from, e.g., the persistence of maternal antibodies. As small RNAs realize the three features simultaneously, a dedicated amplificatory mechanism can ensure transgenerational persistence of the immune effector, without the need for incorporation in the dominant realizer of genetic material—DNA as would be the case for the CRISPR-Cas9 example. But it is still more transient than a genetic system, given that prolonged persistence needs re-occuring triggers to make the inheritance extend beyond 3–5 generations (Houri-Ze’evi et al. 2016).

Given the introduced definition of adaptive immunity, there is no restriction regarding how long immunization can last. It might, however, be safe to say that adaptive immune systems are generally more transient than genetic systems, partly because environmental conditions have directed and specific effects on the material structures of transgenerational immune systems (described so far). At the same time (if restricted to, e.g., 3–5 generations), these structures are not involved in (epi)genetic processes such as genetic assimilation or the Baldwin effect (Loison 2019) and are in that way disentangled from evolutionary adaptation. This is, of course, not to say that strict boundary drawing can ever be managed, but rather tries to bring to the front different aspects of adaptiveness.

\[3\] Here, I only consider “molecular” pathways that ensure persistence, leaving out other potential forms of transmission, such as social immunity (Masri and Cremer 2014).
Conclusion

In this paper, I have examined the relation between genetic and immunological adaptation. For doing so, I have formulated a characterization of adaptive immune systems and analyzed several recently proposed instantiations of potentially adaptive-like immune systems. I have focused on small RNA-based immunity in *C. elegans* to carve out what a transgenerational perspective on immune systems entails regards the distinction of or the fluidity between immunologically and genetically adaptive changes.

This distinction is not only salient for non-vertebrate immune systems but might also be relevant for jawed vertebrate immune systems. Recently, a piRNA cluster targeting endogenous bornavirus-like nucleoprotein elements (EBLNs) in mammals have been discussed as transgenerational immune memory (Parrish et al. 2015). Species with these EBLNs are relatively immune to bornaviral disease, giving rise to the hypothesis that also mammals possess a transgenerational variant of immune memory. This system, however, lies again much more in the vicinity of CRISPR-Cas9 based immunity in bacteria and archaea, given that it also relies on the genetic incorporation of material that guarantees transgenerational immunological memory and thus lies much more in the vicinity of a genetic adaptation than do small RNA-based systems in *C. elegans*, at least those that exclusively operate by maintaining pathogen-derived small RNAs that bear no correspondence in the host genome.

The fact that small RNA-based systems in diverse phyla might show some continuity between the (exclusively) immunological and the genetic might further emphasize the idea that a strict separation between these two domains might not be feasible when we invite transgenerational instantiations of immune systems. I, however, hope to have been successful in providing an updated characterization of adaptive immune systems that summarizes current developments in immunology as well as a means to carving out different aspects of transgenerational adaptivity intended to help conceptualize cases of systems that sit at the crossroads of genetics and immunology. Also, I hope to contribute to recent debates in the small RNA inheritance field, where the notion of a small RNA-based immune system has been mentioned *in passim* but has not yet fully been spelled out (Chaves et al. 2021). The aim is not to make definite calls regarding "membership" but to have a roadmap when trying to understand and classify such processes.

However, while processes might lie between or extend across disciplinary boundaries, it will remain important to analyze the terminology used to describe these processes carefully. Small RNA-based immunity is an excellent example since the phenomenology was investigated in the context of genetics and is mainly adorned with the language of that particular disciplinary context. Small RNAs making their way into immunological discourse might bring with them specific terminologies, such as "acquired," "adaptiveness," or "resistance," which need to be resituated in their new context. It also marks a transition from a "basic research" to an "applied research" context, given that the principal aim of immunology might both historically and currently be best described in understanding,
treating, and curing human diseases. With this disciplinary focus also comes a focus on models that can represent human diseases and thus an emphasis on jawed vertebrate immune systems. The incorporation of small RNA-based phenomena into the immunological canon thus marks a disciplinary transition as well as one regards "paradigm" organisms, necessitating conceptual heavy-lifting to resituated adaptivity guaranteed through small RNA inheritance in the immunological context.

This observation is not only of interest for philosophical and historical investigations into disciplinary situatedness (Hühnefeldt and Schlitte 2018), boundary objects (Star and Griesemer 1989), or scientific repertoires (Ankeny and Leonelli 2016) but also might contribute a fruitful link between the philosophy of immunology and the philosophy of epigenetics. The philosophy of epigenetics has, as of yet, primarily focused on canonical epigenetic marks and inserted into discussions regarding causality (Baedke 2018), evo-devo as well as units of selection (Jablonka and Lamb 2014). Epigenetics has been identified as a means to bridge gaps between biological fields (Nicoglou and Merlin 2017), and small RNAs could be one instantiation of a novel way of bridging immunology with genetics. At the same time, their example shows that the inheritance of acquired traits need not necessarily be conceptualized as cases of evolutionary adaptation and thus might also not necessarily be a means to disprove or vindicate evolutionary theories. It opens the possibility of considering some epigenetic processes as immune processes and, consequently, provokes the question of how to conceptualize immunological and evolutionary individuality if the effectors that negotiate the immunological individual persist transgenerationally. In conclusion, studying alternative instantiations of adaptive immunity helps crystallize both characteristics of adaptive immunity, as well as it clarifies an important issue when it comes to the increasing amount of reports on the inheritance of immune responses, which takes the transgenerational perspective seriously as one that is distinctly immunological and not coextensive with genetic adaptation.

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