Studying immunity at the whole organism level

Sir,

Hauton and Smith (BioEssays 29:1138) make the strong assertion that a whole-organism phenomenological approach to investigating invertebrate immunity is flawed and sidesteps scientific rigour. Their major claim appears to be that we should not study immunity based on observations at the level of the whole organism, and should instead limit ourselves to measuring the levels, regulation and interactions of immune molecules. We do not want to argue against the desideratum of understanding the physiological, biochemical and molecular genetic basis of immune responses but, unfortunately, the case that Hauton and Smith make both misrepresents and misunderstands the evolutionary ecology work that is being carried out on immunity. Consequently, whilst they claim to have discovered a straw house, they have instead erected a straw man.

Immunity can be regarded as a state of having sufficient biological defenses to avoid infection or reduce the consequences of infection. It is by its nature an organism-level phenomenon. The intricate mechanisms that give rise to immunity are interesting and their elucidation can only help in understanding the phenomenon of immunity. For example, measurement of molecules can often be used as a proxy for immunity when it cannot be measured directly at the organismic level. But to argue that we cannot say that an organism has increased immunity unless we have studied the molecule responsible is illogical. We should remember that the phenomenon of immune memory (e.g. as exploited by Edward Jenner in the 18th century) was known and accepted long before the molecular basis of adaptive immunity was understood. So why not study immunity in invertebrates in the same spirit? And if the phenomenon is really based on an as-yet-undiscovered mechanism, then what molecule would Hauton and Smith have us measure? The primacy of mechanistic study is also questionable at the practical level mentioned by Hauton and Smith: would aquaculturalists prefer a drug that actually had a demonstrable effect to reduce disease outbreaks, even if it is not known what molecules are involved, or one that raised the level of a known molecule with no known fitness effect?

Consistently, Hauton and Smith dismiss host fitness measures, such as fecundity or survival, as being irrelevant for the discussion of immune memory. However, precisely because immune memory must have effects on host fitness to either evolve or be eliminated by natural selection, such measures are appropriate. It is ironic that, in several places, Hauton and Smith invoke evolution by natural selection to explain differences in immune responsiveness among individuals. How could this be possible without fitness variation? It is also unfortunate that their criticisms of fitness measures contain glaring technical errors. For example, the suggestion that genotypic differences between *Daphnia* embryos might explain the apparent transfer of strain-specific immunity ignores the biology of this system: *Daphnia* reproduce clonally. We cannot here comment in detail on the many errors in Hauton and Smith's interpretation of adaptive studies, but we do wish to make the general point that showing one thing (e.g. immune priming) is not the same as discussing its biological significance (e.g. possible adaptive value). The fact that we do not yet know the many potential adaptive functions of immune priming does not imply that it can therefore not exist.

Hauton and Smith state that the criticized studies are based on a few individuals and unusual host–parasite associations, and assert that to build a new global theory based on special cases is inappropriate. We agree, and would not attempt such a feat. Nevertheless, we feel that Hauton and Smith ignore that statistically ascertained differences are reported and that, in most of the criticized studies, care was taken to use host–parasite associations that can occur naturally, something which is not always the case in immunological studies. We are lost to understand why studying rats and mice is acceptable as the universal basis for global insights into vertebrate immunity, whilst studying insects and crustaceans represents a limited and special set of hosts. Hauton and Smith further criticize that we and others ignore earlier studies that have failed to show evidence for memory effects. However, some of these earlier studies (cited in the criticized literature) do indeed show different responses upon secondary exposure. These early findings have now been extended, and it is ironic that Hauton and Smith ignore some of this recent work (e.g. Sadd, B. and Schmid-Hempel, P. (2006) Insect immunity shows specificity in protection upon secondary pathogen exposure. Current Biology 16:1206–1210).

If phenomenological observations cannot be easily shoehorned into existing global models of either vertebrate or invertebrate immunity, this should cause us to question such models. Doing so will require rigorous experimental tests and sometimes such experiments will show that the phenomenon can, after all, be understood in terms of well-described mechanisms. Sometimes they may not. Regardless of what immunologists confidently assert in textbooks, we may only be scratching the surface of invertebrate diversity. Thus, instead of disregarding whole organism studies and relying on the status quo, a better solution is working hard to develop immunology for systems showing memory or specificity. As we expand immunology to these cases, it will be important to test hypotheses linked to whatever mechanisms fall under our

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gaze. For example, we could ask if the temporal signature of a primary response is longer or shorter than the rules of biochemistry and physics would suggest. If it is longer, it may have evolved to cope with secondary encounters; it may be adaptive.

Thus, we suggest that the effort to elucidate the mechanisms of apparent adaptive immunity should not be constrained by the idea that the only system deserving of the term ''adaptive immunity'' is one composed of clonally derived lymphocytes and MHC molecules. Similarly, we suggest that this effort not be constrained by the use of experimentally convenient but biologically irrelevant elicitors (e.g. *E. coli*), but instead be directed towards naturally coevolving systems where specificity will be fine-tuned and relevant.

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