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Academic-industry partnerships in addressing nutrition – *[Infection-immunity-inflammation]* interactions

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The interaction between nutrition and infection is a key determinant of human health. Traditionally the interaction has centered on the role of nutrients in defining host defenses and the impact of infection in defining nutritional needs and status. Over the past decades the interaction has expanded its scope to encompass the role of specific nutrients in defining acquired immune function, in the modulation of inflammatory processes and on the virulence of the infectious agent itself. More recently the role of micronutrients and fatty acids on the response of cells and tissues to hypoxic and toxic damage has been recognized suggesting a fourth dimension to the interaction. The list of nutrients affecting infection, immunity, inflammation and cell injury has expanded from traditional protein-energy supply to several vitamins, multiple minerals and more recently specific lipid components of the diet. The promise of nutrition in the defense against infection, inflammation and tissue injury has spawned a thriving pharma-nutritional supplement industry and the development of novel foods that require appropriate evaluation of efficacy, safety and effectiveness relative to costs. Academics need to aware of the ethics and the pitfalls in the interaction with industry; conversely industry has to define its role in the process of bringing new knowledge to useful products. The process needs to be interactive, transparent and clearly place public interest above all other considerations.

Traditionally, the study of the interaction between nutrition and infection (as *"the first I"*) has encompassed the role of infection in defining nutritional status and the role of nutrition in determining host defence mechanisms. This concept emerged from multiple observations in developing countries (India, Africa and Central America) was captured in a classic monograph by Scrimshaw, Taylor and Gordon[1]. Young children became infected, ate less and lost more nutrients than normal, and stopped growing. Thus the relationship between the diet and nutritional status was considered as a triangle where the interaction of diet and infection defined nutritional status. The realisation that case fatality from infections more than incidence was affected by nutritional deficits lead to research on the role of nutrition on specific components of host defence systems. The epidemiologic and laboratory work of Mata in Central America[2], Chandra in India[3], and Suskind in Thailand[4], amongst other research workers served to firmly establish the critical role of protein energy malnutrition in defining not only cellular and humoral immune function but also non-specific host defence systems. Further methodological advances facilitated the study of cellular and molecular mechanisms underlying the initial clinical observations derived mainly from malnourished infants in poor countries[5]. These observations were soon followed by studies of malnourished hospitalised adult patients in industrialised countries demonstrating that the effects were of great significance to both adults and children, and had a major impact on global health[6]. The progressive understanding that protein-energy malnutrition (PEM) was not only protein and energy deficiency but also involved insufficiencies in the cellular supply of multiple micronutrients, served to highlight the importance of specific micronutrients (vit A, Fe, Zn and Copper) and their respective carrier proteins (retinol binding protein [RBP], transferrin, albumin and ceruloplasmin) on specific and non-specific components of the immune response[7,8]. This knowledge led to the need to include immunity as the link in the relationship between nutrition and infection (*"the second I"*). The scientific impetus generated by the emergence of knowledge about the immune system and the associated myriad of effects and interactions, mediated by local tissue and circulating hormones, set the stage for a new layer of complexity for nutritional effects on infection, beyond the traditional immune response, to reveal itself[9]. The linkage chain now included nutrition, infection, immunity and the inflammatory response. The role of classical nutrients in defining inflammation was a bit harder to establish; since cytokines, genetically coded, potent circulating peptides that act in minuscule amounts, left little room for a convincing effect of diet on the inflammatory response. In fact, traditional essential nutrients such as tocopherol, retinol and zinc do not modify cytokines in their actual aminoacid composition or serve as building blocks to form them, but act to regulate the process, modulating the intensity of the responses that define the inflammatory process. Parallel advances in lipid biochemistry, with major implications for nutrition, contributed to the resolution of this issue. The fact that essential fatty acids and the product of their metabolism (arachidonic, eicosapentaenoic and docosahexaenoic acids) were both key

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components of cell membranes and at the same time served as precursors for mediators of the inflammatory and the immune response served to spark renewed interest on the potential influence of nutrition on inflammatory processes. This time the effects of nutrients were centre stage in the inflammatory phenomena; nutritional epidemiology considering comparative studies of the high *n*-3 fatty acid Eskimo diet vs. the high *n*-6 fatty acid western diets served to highlight the importance of the balance of these mediators and the contrast of the effects illustrated the potential health gains from modulating the quality of the lipid intake[10,11]. This knowledge paved the way for the inclusion of inflammation as "*the third I*" in the relationship between nutrition and infection. We have only begun to elucidate how lipid moieties and micronutrients interact, both in their genuine nutritional role and also as part of the oxidant/antioxidant system that is both causally and consequentially related to infection, immunity and inflammation. The role of tocopherols as key antioxidants in promoting normal host defences but also in compromising phagocytes and the bacterial killing capacity of leukocytes when in excess serve to underpin the scientific basis of the epidemiologic observations. The demonstration of an open U shaped risk versus dose response can now be explained, too little vitamin E compromises the immune system while excess tocopherol interferes with superoxide production, leading to increased mortality[12,13]. Some may even suggest the need for a "*fourth I*" considering that nutrients also modulate injury as an end point of hypoxic or toxin mediated cell damage. The newly discovered resolvins derived from essential lipids are opening the way for new thinking on how dietary components can prevent further injury after infections, microbial toxins and hypoxia. In fact, the demonstration that 10,17S-docosatriene is able to reduce post hypoxic brain infarcts and release of re-perfusion injury mediators, offers new hope into ailments that up to now have proven fairly resistant to preventive or curative actions. In addition, knowledge of how docosahexaenoic acid DHA and related compounds are able to block the effect of platelet activating factor PAF and other cytokine tissue injury mediators, limiting inflammation and injury after endotoxin-lipopolysaccharide induced injury, creates new opportunities to modulate these phenomena under health and disease conditions[14,15].

Academia-Industry Partnerships: learning from past and recent experience

How do potential academic-industry partnerships (AIPs) fit into the picture of Infection-Immunity-Inflammation interactions? Based on the brief review presented in the preceding section it is clear that there are multiple business opportunities related to food products or specific food components that may affect the range of potential interactions described. Given the limitations of space, I will not discuss in this paper the potential health effects of essential and non essential nutrients in foods. In fact the agenda and scientific programme of the meeting, the industry sponsorship and the exhibitions provide a clear indication of the health significance of the science generated in the field on nutrition-infection-inflammation-injury. The application of this science to the design of products and to the appropriate evaluation of the potential risks and benefits derived from their use is clearly an area of interface between scientists, industry and regulators. The purpose of this paper is to address selective issues that should be taken into account in advancing partnerships that are of interest to the public in terms of their health and well being while preserving the essence of the science we conduct in concordance with the public trust placed in us as scientists.

Evaluation of health effects of foods and food components

Foods used for special medical purposes are traditionally prescribed by physicians to meet specific nutritional requirements in patients who are malnourished due to disease and/or poor diet. These products are used under medical supervision, and their indications for use are based on sound clinical evidence of efficacy and safety. A wide array of such products exists, and their indications typically have evolved as research into their beneficial effects is conducted[16,17].

Functional foods and novel ingredients are food products used to promote optimal health. The composition of these products is not necessarily regulated, making for a broad compositional diversity among products. The term 'functional foods' has been defined to mean foods which demonstrate a beneficial effect beyond the obvious nutritional effects in terms of provision of both essential and non essential nutrients[17]. These effects might include an improved state of health and well-being or a reduction in the risks associated with certain diseases. Novel ingredients are also being evaluated for potential use as therapeutic agents. Pre- and Probiotics are examples of novel ingredients that can modulate the intestinal microflora; phytoestrogens and carotenoids are other examples of novel ingredients with potential health benefits for bone health and cancer risk. Food components that affect lipid and carbohydrate metabolism, and defence against oxidative damage are also of interest. There is certainly a place in medical and public health practice for functional foods that have been tested rigorously and are proven safe and beneficial in promoting health and well being, or in preventing functional losses. Some of the important targets for their use include child growth and development, bone health and immune function especially during early life and in ageing. Because the concept of functional foods and novel ingredients is relatively new, regulatory frameworks or guidelines to assess efficacy and effectiveness are often poorly defined or in some cases not available. While there is some agreement that functional food products and novel ingredients should be evaluated for efficacy and safety by formulating and testing specific hypotheses, few guidelines are currently in place except for those where health claims are being considered. If many of the products in the market were examined, few would have solid and sufficient evidence of effectiveness in terms of disease prevention under real world conditions although most would meet safety standards[17].

Industry and academia are increasingly coming together to create products which will meet specific consumer demands or perceived needs. An admittedly oversimplified view of the relationship between academia, industry, and consumers is that academia is driven by science, industry by profit, and consumers are driven by the benefits they derive from the

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products produced by industry. It is important to look at how successful partnerships between academia and industry are formed, and what are the responsibilities of each partner in taking products from scientific innovation to product development and to their final place in the food supply. Typically, academia and industry first come together to develop a scientific concept in response to a consumer need, whether established or perceived. The scientific basis for innovation serves to focus product development as well as to determine what consumer education efforts will be necessary to ensure that the product will then be accepted and in demand. Consumers often have insufficient knowledge of the many factors that determine their nutrition, health and well being. They may not know much about the role of the specific nutrients included in a product until they learn of the potential benefits of that product. Academic-Industry Partnerships can play an important role in disseminating and supporting consumer education. Consumers are commonly rightfully skeptical of information coming from a source that stands to make a profit, be it from the private or the academic sector. This reinforces the role for academia in providing independent scientific advice and education to consumers. It is worth reiterating that no matter how successful the marketing and consumer education efforts are by themselves, unless the innovation has a strong scientific base, sooner or later it will fail. Once the concept has a well established scientific base, the potential products can be considered. However before actually formulating a product for testing, the safety of the potential product must be thoroughly considered. This is a necessary but insufficient step, since in the final analysis any purchase involves a cost benefit assessment from the viewpoint of the consumer. The fact is that unless consumers perceive that the gain they will obtain from consuming the product is greater that the monetary outlay they make, they will not buy it. These assessments are necessary before taking the product concept any further. Academia can play a major role in evaluating safety risks and perceived or real benefits to consumers. Here is where sound research methods and well validated results are essential. The academic and industrial partners should develop a database to support not only the efficacy and safety of all products under development, but also the effectiveness which can only be measured under real life conditions. The evaluation should be continued after the product is placed in the market. As part of the risk benefit analysis, industry must estimate costs and profits to determine if the product concept is economically viable and if it will yield a profit. Investors will explore alternative options if, on final analysis, the product is not sufficiently profitable or if the opportunity costs are excessively high[16].

Post-marketing surveillance of food products is associated with both opportunities and challenges. Data obtained after product launch is complementary to the kinds of data that can be obtained from pre-market clinical trials. For instance, a higher number of people will be exposed to the product for a longer duration in post-marketing studies, thus the impact can be assessed beyond biomarkers of disease and measured by prevention of more relevant endpoints. This need not consider only clinically relevant effects but also prevention of disability [loss of disability adjusted life years (DALYs)] or quality of life indicators [quality adjusted life years (QUALYs)]. Interactions with other dietary or lifestyle factors that may have been difficult to evaluate in the pre-market trials may surface in the post marketing studies. The actual use of products often differs from their intended use, providing an opportunity to look at product consumption in a more realistic way. The observation of actual product consumption allows identification of potential risks and evaluation of potential benefits in specific sub groups that were not identified prior to the introduction to the market. Post-marketing surveillance studies, although typically designed to monitor adverse reactions of drugs, can also provide an opportunity to study product effectiveness, and assess the changes in dietary patterns and nutritional status that can be related to the entry of a product to the market. There are two main types of post-marketing studies; passive or active surveillance studies. One example of passive surveillance would be a toll free telephone number for consumers to call and provide their opinions on a product as well as record any adverse reactions they had experienced. The utility of these studies for food products is limited, because the studies rely on voluntary reports from consumers and health professionals. The characteristics of individuals who take the time to call in may be very different from those who do not; in addition, it is very difficult to establish a true causal link from passive surveillance. These studies thus serve mainly to alert for potential problems; nevertheless they are important to monitor since it serves to identify the impact of concurrent events that affect consumers, such as media reports or adverse publicity that can induce surges in feedback which can then be put into perspective. Active surveillance involves either observational or experimental studies. While there is a great deal of expertise in conducting active nutritional studies that examine the relationship between food intake and health effects, the experience is primarily with generic foods and not with branded products. Evaluating individual consumption data and population consumption data is quite different; each requires a distinct methodology to measure the outcome parameter. Lack of data on novel food ingredients, presumably due to lack of information on use, complicates these evaluations. A narrowly regulated application, as is the case with fat replacers which may be used in only a few products, makes intake easier to assess. In contrast, genetically modified foods such as soy, despite best efforts, are not really traceable. Observational studies themselves are subject to bias because individuals have chosen to use the product in question. The individual who uses a novel food may have very different characteristics from one who does not choose to. Confounding lifestyle factors must thus be considered. Another major challenge in active surveillance is the large population and long time period required; the cost can be well beyond what any single company may be willing to bear[16]. However, since long term outcomes are of greatest interest, the studies must also be of sufficient duration, with a large sample size and must ensure subjects are not differentially lost to follow up. The best epidemiological model for this type of evaluation is a cluster randomised controlled trial in which the observation is based on the community and not on the individuals in isolation. We are presently testing several dietary and public health interventions using this approach[18,19] (Table 1).

Table 1. Characteristic of Controlled Evaluation Study

Study Aspect	
Hypothesis	• All studies must be hypothesis-driven, with the hypothesis as the basis for a potential claim
Study Design	• Blinded, randomised, parallel group or crossover, appropriate exclusion criteria, study approved by ethics committees
Patient Population	• Product must be effective in the general population or a large, at-risk population, subjects should be randomly assigned and with sufficient number to secure good match between groups
Sample size	• Sufficient number of subjects to secure not only significance of outcomes related to efficacy but also identify changes in prevalence of adverse effects.
Outcome	• Target function needs to be beyond adequate nutrition, impacting health and well-being or reduction of risk for disease
Efficacy Evaluation	• Relies on biomarkers correlating to an endpoint or intermediate markers representing an endpoint relevant to health

modified from([16]).

Relationship between Academia and Industry

While academic and industrial partners may find areas of overlapping interest and competence, the areas of core competence for each should be established early on. For example, the industry partner should be solely responsible for issues related to profit and business development. If extensive and expensive population studies are needed to prove efficacy and effectiveness, industry may need to form broad alliances or partnerships to develop the necessary evidence to comply with progressively complex regulatory demands. As consumers gain greater influence on food and nutrition policy, the regulatory framework needs to balance the industrial interest for profit with the demand by academic advocates to protect public health interests. This tension has special relevance in the setting of limits for health claims or other marketing schemes that in fact may sometimes conflict with dietary guidelines set as a basis for consumer education and health promotion. Academia has a clear role in developing the scientific concepts, defining the standards for what constitutes evidence, conducting the necessary research to document efficacy and cost effectiveness, providing independent information to regulatory bodies and ultimately to consumers. The academic partner should keep in mind that sufficiently large sample sizes are necessary for valid clinical trials of efficacy. Moreover the ultimate measure of benefit is not only effectiveness but cost effectiveness that considers if resources are being well spent in relation to the benefits obtained. These considerations are critical in taking the results from one setting to another; a product may be effective in populations that are receiving inadequate diets but may confer no benefit and maybe even harm populations that are well fed. The cost of a functional food relative to foods that supply the protective elements naturally for equal benefits may not justify their introduction. These types of evaluations commonly require collaborations between academic groups in order to run the necessary large multi-centre, multi-sites studies, considering biological impact as well as economic costs to consumer[16].

Public interest rather than commercial interest must guide the product development process for academic-industry partnerships to be successful. The determination of what is in the public interest should not be left to the individual judgment of each partner, but should be addressed globally, with consideration given to the following concerns.

- It should be clearly established that the product should benefit not only the industrial sector who stands to profit but also the consumer who will be addressing a real need.
- Under no circumstances should information be withheld from the public because it conflicts with industry's financial gain or other profit-related motives.
- Weak, unsubstantiated, science should never be used as a basis for product development or promotion.
- The regulatory process should not be short-circuited in the interest of getting a product rapidly on the market.
- Patents should be held institutionally (industry or academic institutions) rather than by individuals in order to preserve impartiality by academic or industry researchers in judging the evidence from research studies[20,21,22].

It should be noted that academic researchers who retain greater independence from their industrial partners achieve higher academic standing. A survey-based study demonstrated that the most effective and productive researchers in the USA get less than half of their funding from industry[23]. When academic researchers in the USA receive more than two thirds of total funding from industry they tend to be less productive and their articles have less influence in their respective fields. Over the past decade, norms for public disclosures of competing interests, real conflict of interests and potential for perceived conflict of interests have been progressively implemented by scientific journals, universities, national governments and international agencies. These norms apply to the dissemination of scientific information, the work of technical experts, scientific panels that review evidence or establish recommendations with public or social implications[24,21,22,25].

What can be done in practice to facilitate successful academic-industry partnerships?

One objective of AIPs is to define the ways to optimise the development and launch of new, beneficial products and to identify factors which hinder the process. The role of

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research in innovation, and the roles of industry, academics, expert committees, regulatory bodies, and physicians and consumers in the process leading from innovation to implementation must be examined in order to identify factors that facilitate or impede the process. The key to successful development of new foods and ingredients is to remain focused on the interest of the consumer, because functional foods that are not consumed can serve no healthful purpose, and no profits can be made. Industry serves many functions in the development of food products, including the generation of ideas and knowledge on consumer needs, and the provision of funding and/or facilities to conduct the research.

Much of the tension between marketing professionals (MP) and scientists arises from the conflicting desire of the scientist to methodically determine how a novel food product can best be used, and the desire of the MP to quickly and profitably bring new products to the widest market possible. One resolution is for both scientists and marketing groups to remain focused on the needs of the consumer as the target for both research and sales. One of the challenges in getting consumers to accept novel functional foods and ingredients is that the novelty that is appealing may also breed suspicion. In other words, the goal must be to come up with products that fulfill a consumer need but that does not cause excessive fear such that the product is deemed too novel to be trusted. Consumer education is essential in creating a level of trust; building brand confidence allows the consumer to identify with the product and feel comfortable using it. Industry must play a large role in accurately relaying scientific information to the consumer, so that the popular media is not the consumer's only source of information.

Controlled studies to assess the health benefits of specific foods should be based on a hypothesis that can be rigorously tested using randomised, long term trials with predetermined efficacy and effectiveness outcomes. Ideally, this would involve use of cluster randomised designs providing data from different settings, collected in a standardised way so that pooled data from multiple sites can be used to assess effectiveness and safety.

Good research is the only sound basis for a successful functional food product; having an effective way to communicate information concerning beneficial functional foods to consumers and making sure the foods produced are targeted to a discerning consumer base is equally critical. Since industry ultimately brings products to market, it is important to determine what industry can do to develop functional foods that both benefit the public interest and are profitable. We do need strong science to back up claims. Regulators certainly have a role in terms of defining how much science is sufficient to allow for health claims. Regulatory bodies need to protect the consumer without discouraging innovation. Regulatory legislation to meet these goals is part of the process, but less restrictive ways to promote innovation are also needed. A more useful approach is to have a transparent regulatory process where regulatory bodies, industry, academia and the public interact in the development of guidance for the introduction of new food products, and where product development is an iterative process where products can be re-evaluated and refined even after they are marketed. The establishment of national food standards agencies in most European countries and in the EU region demonstrates that this in fact is feasible and of benefit to both industry and the public alike.

Finally we must also acknowledge that in the real world there are conflicting interests between scientists, marketing and business interests, and the public. It may appear to some that the conflict of interest issue is often over-emphasised in public discussions, and discussions among academic colleagues, however recent experience demonstrates that unless these issues are addressed openly the whole foundation of public trust suffers[25–27]. How investigators that participate in industry partnerships address the following issues, serves to illustrate the nature of the potential problems:

1. Work with their institutions to ensure requirements are fulfilled and relationships are fairly and effectively reviewed and overseen?
2. Address problems related to access, analysis, and dissemination of research information, data, and materials in industry relationships?
3. Operate with transparency and accountability in industry consulting relationships (consulting, advisory board membership, funding for travel to meetings and conferences)?
4. Address conflict of interest issues in their entrepreneurial activities (involvement in start-up companies, patents and technology licensing)?
5. Minimise the negative impacts of those relationships on training and educational activities?
6. Protect human research participants against risks to their health or personal integrity?

These problems are real and must be addressed proactively and openly by academia and industry alike as suggested by the recent FASEB recommendations summarised in (see box 1)[28]. We also need to interpret what is in the public interest by having a forum for open discussion which includes the public. The public and the consumer must be invited to enter the debate. This is already being done in many countries by consumer interest groups, academic advocates and the government. National and international regulatory agencies should also be involved. Infant formula is a good example of how public interest in the 1960's brought about the code of infant formula marketing, which continues to monitor the commercial practices and marketing conduct of industry. We must keep the relationship between industry and academia transparent and open for review, because in the final analysis nobody but the public can defend its own interests.

Conflict of interest statement

RU is President of the International Union of Nutritional Sciences (IUNS). He receives research funding from Wellcome Trust and from Chilean National Science and Technology Fund. He is an ad hoc consultant to the UN, bilateral and private sector; fees for these activities are handled in compliance with IUNS rules for officers. The author has no conflicting interests regarding the content of this paper.

BOX 1. FASEB guiding principles to aid investigators in addressing critical issues in interactions with industry. (modified from FASEB 2006[28])

1. Investigators have a responsibility and commitment to conduct scientific activities objectively and with the highest professional standards.
2. The primary responsibility of full-time investigators is to the institution. Outside activities shall complement, not compromise, institutional responsibilities.
3. It is appropriate and beneficial for academic institutions to develop and enforce their own mechanisms of review and oversight of investigator relationships with industry.
4. The academic community can and shall monitor itself through peer review of industry relationships. Institutional committees that include peer members from the same institution are appropriate and effective in reviewing disclosures of investigators' industry relationships.
5. Investigators want and need clear guidance, efficient processes, and adequate support mechanisms from their institution throughout their participation in industry relationships.
6. Investigators shall have access to, and be involved in the analysis and/or interpretation of all data generated in the research.
7. Mutual understanding of constraints, principles, and policies regarding access, analysis, and dissemination of research information, data, and materials among investigators and their students and trainees, institutions, and sponsors is beneficial.
8. Investigators shall not enter into agreements with companies that prevent publication of research results. Pre-publication review by an industry sponsor shall occur in a timely manner (no more than thirty to sixty days) so as not to unnecessarily delay study publication.
9. Investigators shall be aware of and adhere to individual journal policies on disclosure of industry relationships.
10. Consulting and advisory board relationships shall be carried out in a transparent and accountable manner and be disclosed as they are initiated.
11. When investigators have consulting relationships with an investment firm related to their area of expertise, all parties shall be aware of the specific circumstances involved.
12. Investigators shall not use public funds to the benefit of a company, unless this is the explicit purpose of the mechanism used to fund the research (e.g., Small Business Innovation Research and similar grants).
13. When investigators own significant equity in a company with which research is conducted, all parties shall be aware of the special circumstances involved.
14. When holding a significant role in a start-up company, investigators shall be guided by agreed-upon limits to the scope of the relationship.
15. Investigators shall be aware of and adhere to requirements of public funding sources related to disclosure of inventions. Investigators shall adhere to patent law and institutional requirements.
16. Investigators shall not seek to influence their institution's technology transfer decisions for personal gain.
17. A mentor's outside commercial interests shall avoid impeding a trainee's timely progress toward his/her degree, restricting a trainee's right to publish his/her dissertation research in a timely manner, compromising a trainee's career progress, or restricting a trainee's freedom of inquiry.
18. Mentors and institutions should make trainees aware of their rights and responsibilities in industry relationships.
19. Investigators shall regard all significant financial interests in research involving human subjects as potentially problematic and thus requiring close scrutiny.

References

1. Scrimshaw NS, Taylor CE & Gordon JE (1968) Interactions of nutrition and infection. *Monogr Ser World Health Organ* **57**, 3–329.
2. Mata LJ, Kromal RA, Urrutia JJ & Garcia B (1977) Effect of infection on food intake and the nutritional state: perspectives as viewed from the village. *Am J Clin Nutr* **30**, 1215–1227.
3. Chandra RK (1984) Parasitic infection, nutrition, and immune response. *Fed Proc* **43**, 251–255.
4. Sirisinha S & Suskind R (1974) Host defenses in protein-calorie malnutrition. *J Med Assoc Thai* **57**, 197–206.
5. Chandra RK (1996) Nutrition, immunity and infection: from basic knowledge of dietary manipulation of immune responses to practical application of ameliorating suffering and improving survival. *Proc Natl Acad Sci USA* **93**, 14304–14307.
6. Bistrian BR, Blackburn GL, Vitale J, Cochran D & Naylor J (1976) Prevalence of malnutrition in general medical patients. *Jama* **235**, 1567–1570.
7. Beisel WR (1977) Magnitude of the host nutritional responses to infection. *Am J Clin Nutr* **30**, 1236–1247.
8. Gershwin ME, Keen CL, Mareschi JP & Fletcher MP (1991) Trace metal nutrition and the immune response. *Compr Ther* **17**, 27–34.
9. Keusch GT (1998) Nutrition and immunity: from A to Z. *Nutr Rev* **56**, S3–S4.
10. Mascioli E, Leader L, Flores E, Trimbo S, Bistrian B & Blackburn G (1988) Enhanced survival to endotoxin in guinea pigs fed IV fish oil emulsion. *Lipids* **23**, 623–625.
11. Yaqoob P & Calder PC (1993) The effects of fatty acids on lymphocyte functions. *Int J Biochem* **25**, 1705–1714.
12. Meydani SN, Meydani M, Blumberg JB, *et al.* (1997) Vitamin E supplementation and *in vivo* immune response in healthy elderly subjects. A randomized controlled trial. *JAMA* **277**, 1380–1386.
13. Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ & Guallar E (2005) Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* **142**, 37–46.
14. Mukherjee PK, Marcheselli VL, Serhan CN & Bazan NG (2004) Neuroprotectin D1: a docosahexaenoic acid-derived docosatriene protects human retinal pigment epithelial cells from oxidative stress. *Proc Natl Acad Sci USA* **101**, 8491–8496.
15. Schwab JM, Chiang N, Arita M & Serhan CN (2007) Resolvin E1 and protectin D1 activate inflammation-resolution programmes. *Nature* **447**, 869–874.
16. Leathwood P, MacLean W & Uauy R (1999) The role of industry in bringing foods for particular nutritional uses (PARNUTS) to the market. *Eur J Clin Nutr* **53**, Suppl 3, S9–13.
17. Roberfroid MB (2000) Concepts and strategy of functional food science: the European perspective. *Am J Clin Nutr* **71**, 1660S–1664S, discussion 1674S-1665S.
18. Dangour AD, Albala C, Aedo C, Elbourne D, Grundy E, Walker D & Uauy R (2007) A factorial-design cluster randomised controlled trial investigating the cost-effectiveness of a nutrition supplement and an exercise programme on pneumonia incidence, walking capacity and body mass index in older people living in Santiago, Chile: the CENEX study protocol [ISRCTN48153354]. *Nutr J* **6**, 5 July 2007.
19. Dangour AD, Clemens F, Elbourne D, *et al.* (2006) A randomised controlled trial investigating the effect of n-3 long-chain polyunsaturated fatty acid supplementation on cognitive and retinal function in cognitively healthy older people: the Older

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People And n-3 Long-chain polyunsaturated fatty acids (OPAL) study protocol [ISRCTN72331636]. *Nutr J* **5**, (31 August 2006).
20. Culliton BJ (1982) The academic-industrial complex. *Science* **216**, 960–962.
21. Jorgensen AW, Hilden J & Gotzsche PC (2006) Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review. *Bmj* **333**, 782.
22. Smith R (2006) Conflicts of interest: how money clouds objectivity. *J R Soc Med* **99**, 292–297.
23. Blumenthal D, Campbell EG, Causino N & Louis KS (1996) Participation of life-science faculty in research relationships with industry. *N Engl J Med* **335**, 1734–1739.
24. Blumenthal D (2003) Academic-industrial relationships in the life sciences. *N Engl J Med* **349**, 2452–2459.
25. Margetts B (2006) Stopping the rot in nutrition science. *Public Health Nutr* **9**, 169–173.
26. McCrary SV, Anderson CB, Jakovljevic J, Khan T, McCullough LB, Wray NP & Brody BA (2000) A national survey of policies on disclosure of conflicts of interest in biomedical research. *N Engl J Med* **343**, 1621–1626.
27. Stossel TP (2005) Regulating academic-industrial research relationships–solving problems or stifling progress? *N Engl J Med* **353**, 1060–1065.
28. Federation of American Societies for Experimental Biology (FASEB) 2006 Shared responsibility, individual integrity: scientists addressing conflict of interest in biomedical research http://opa.faseb.org/pdf/FASEB_COI_paper_7x06.pdf accessed june 30, 2007.

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