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Editorial

Connecting science past and future

I recently read the article on protein A pretreatment, alleviation of inflammatory reaction, and evaluation of biosafety *in vivo* in the March 2016 edition of the *Journal of the Chinese Medical Association*.[1] I applaud the renewed research on *Staphylococcus aureus* protein A (SPA), and would refer to the very pertinent previously published information on SPA efficacy and toxicity. While SPA in rats and mice does not bind a complement fixing class of antibody and is safe at greater doses, this is not the case in guinea pigs and humans. SPA at a dose of 1 mg/kg can cause a lethal anaphylactoid reaction in guinea pigs and possibly in humans.[2,3] U.S. Patent No. 5,189,014 (Cowan) describes using Fc receptor (FcR) to treat diverse pathologies having an FcR-mediated immune component, including bacterial and viral infections, autoimmune disorders, transplant rejection, and cancer.[3] The patent and citations show SPA toxicity is a concern but manageable and demonstrate the reduced toxicity of monovalent SPA (MSPA) fragments having only a single Fc antibody binding site. This patent and information derived from earlier studies and their related publications helped to pioneer the field of receptors as drugs and establish the role of FcRs as effectors of immune regulation that can influence gene expression, cellular differentiation, viral replication, and malignant transformation.[4] The field of FcR-based drugs remains a focus of contemporary science long after the original discovery.[5]

Previous work on FcR immunotherapy suggested a broad range of immune regulatory effects on endogenous FcR-mediated immunity, and potential therapeutic effects in many diseases with associated abnormal FcR-mediated immunity.[3,4] For example, the early work by Coley showed antineoplastic activity of bacterial extracts likely to have contained FcR-like proteins.[6] Interestingly, sera perfused through SPA columns were observed to have antineoplastic activity in animal models and human patients, but the antineoplastic action of the perfused sera was lost as the SPA column technology improved to provide better binding of SPA to the support matrix and less leaching of SPA.[7] Systemic injection of SPA in animal models also produced antineoplastic results.[3,4,8] However, to my knowledge, the concept of systemic SPA−FcR immunotherapy with known injected doses was never tested clinically in human patients. At the time of our early publications, only SPA−FcR activity was known and proposed as the best mode of action.[3] Other binding actions of SPA such as Fab antibody "superantigen" are now known. Many of the broad observations we made could be caused by or influenced synergistically by binding mechanisms other than SPA−FcR. SPA deserves new study that brings together past discovery and modern technology. Exciting progress in this direction has been made by Protalex, Inc., which is developing immunotherapies using MSPA to treat pathological inflammatory responses and autoimmune diseases.[9]

Much of the current drug development science and technology remains narrowly focused on single sites of drug action, even as we apply vastly increased volumes and complexities of data from arrays, algorithms, and analyses of genes and molecules. The focus on single sites of action ignores biological redundancy and the multiple pharmacological actions of many drugs and molecules, SPA included. Complexity can sometimes defeat purpose and hide a simple, straightforward, and cost-effective insight for efficacy. Modern medical drug discovery has its roots in traditional medicine that lacked mechanistic knowledge but was fully aware of its efficacy. A better marriage of modern and traditional medicine might better link efficacy to information and collectively provide avenues to more beneficial therapies, and ultimately yield a deeper understanding of the relationship of biological processes underlying efficacy.

FcR-mediated immunity and inflammation occur in most injuries, insults, and diseases. Serious harm can result when inflammatory responses become pathological. The multithreat medical countermeasure (MTMC) hypothesis proposes that pathological inflammatory responses are a major common mediator in the pathology of many damaging chemical insults, and similar mediators, mechanisms, pathways, and cell processes are associated with trauma, cancer, and a multitude of other diseases.[9] Known anti-inflammatory drugs and other drugs with secondary anti-inflammatory pharmacology can be used in combinations that act synergistically to provide therapeutic effects.[9,10] Furthermore, the physiological to pharmacological spectrum of diet, dietary supplements, traditional medicines and herbs, and drugs can be used singly or in synergistic combinations to alter inflammatory response and provide new pathways to therapeutic treatments.[10] In this respect, biomarkers are a cornerstone of MTMC development, as they allow measuring and evaluating relevant "situational" immunity such as hypercytokinemia that may be critical to both health and pathology, and efficacy and toxicity.

Mechanistically, the "cytokine storm" (hypercytokinemia) is associated with soluble mediators, receptor−ligand binding,

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biochemical pathways, gene activation such as nuclear factor-κB, and a host of cell−cell interactions that influence inflammation and related cellular processes such as apoptosis, and provides some commonality of mechanism for a variety of pathologies.[9,10−12] Inflammatory pathology may be as varied as a potentially acutely lethal systemic reaction, an arthritic joint, a cutaneous blister caused by the chemical warfare agent sulfur mustard, or neuronal damage associated with trauma, or Alzheimer's disease. The potential of pharmaceutical approaches in treating hypercytokinemia-induced pathology is limited by the lack of anti-inflammatory drugs that effectively influence these harmful immune responses. Applying MTMC concepts to identify combinations of drugs and compounds that synergistically inhibit hypercytokinemia by systematically screening levels of key biomarkers of inflammation may help overcome this limitation.[9,10] Such biomarkers include genetic components, cell populations, cellular processes such as apoptosis, proinflammatory cytokines [e.g., interleukin-6 (IL-6), IL-8], anti-inflammatory cytokines (e.g., IL-10), and more generalized biomarkers of inflammation such as complement-reactive protein.

One of the articles I have encountered that best merges historical reflection and modern perspective is by Coventry and Ashdown.[13] They point out that the incidence of complete clinical responses for most metastatic cancers has remained constant and low between 5% and 10% for many decades, and that this same constant, low rate of success holds for all treatment modalities—chemotherapy, radiation, surgery, or other means. They suggest that "Inflammatory and immune responses appear intricately associated with, if not causative of, complete responses induced by divergent forms of cancer therapy…leaving inflammation and immune system stimulation as a final common denominator across all of these mechanisms of cancer therapy." If such immune mechanisms and biorhythm cycles were coupled with anti-inflammatory MTMC to reduce hypercytokinemia, one wonders how this might affect clinical responses for metastatic cancers and perhaps many other pathologies and diseases.

The process of discovery has a vital role in harmonizing traditional and modern medicine, efficacy, and information. The failure of modern science to connect with its history causes inaccuracy and breaks the continuity of ideas. This also yields false accreditation of discoveries and can weaken or destroy patent intellectual property. A chief culprit is the vast scope of scientific information. Technology moves fast, rendering anything not published within the last half decade often unread, uncited, and unknown. Time to read and reflect on published scientific literature, including patents, is a scarce luxury that most contemporary scientists do not have in their "produce or perish" enterprise that generates even more new information. Scientists value and rely on the record of discovery, but oversights and errors in citation are readily replicated in the scientific literature without much notice or correction. This can prevent the broader distribution of valuable insights and information, cause duplication of effort, and retard progress in science. Harmonizing the record of discovery in the marriage of traditional medicine and modern science would promote new insights and discoveries in medicine and science.

Conflicts of interest

The author declares that he has no conflicts of interest related to the subject matter or materials discussed in this article.

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