IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

2014; 4(12): 1209-1210. doi: 10.7150/thno.10503

Editorial

Multidisciplinary Efforts Driving Translational Theranostics

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Received: 2014.09.07; Accepted: 2014.09.08; Published: 2014.09.19

Abstract

This themed issue summarizes significant efforts aimed at using "biological language" to discern between "friends" and "foes" in the context of theranostics for true clinical application. It is expected that the success of theranostics depends on multidisciplinary efforts, combined to expedite our understanding of host responses to "customized" theranostic agents and formulating individualized therapies.

Key words: proteomics; bioinformatics; RNA interference; gene delivery; theranostics

Diagnostics have lent a heavy hand in guiding medicine toward more informed treatment and management in what is a rapidly expanding discipline termed *theranostics* [1, 2]. In the last decade, academic researcher and pharmaceutical companies have accelerated the search for markers for disease subtypes, development or refinement of functional biomaterials, and more personalized treatment strategies, signaling the promise of this discipline for clinical translation [3, 4]. Advancements in the fields of chemistry, molecular biology and engineering have facilitated the design, development, and implementation of sophisticated and integrated systems for health care. Theranostics is being applied to explore variability in therapeutic responses in patients to different medications, vaccines, or lifestyle modifications prescribed by physicians [5]. Despite its enormous potential to drive the evolution of precise diagnostic agents and drug delivery at the cellular and molecular level, theranostic medicine still faces challenges, chief among them are the formidable biological barriers such as host immunity [6]. A better understanding of these barriers will inform development of more nuanced theranostic agents that are, for example, capable of navigating effectively and safely toward their intended sites. This special issue summarizes significant efforts aimed at using "biological language" to discern between "friends" and "foes" in the context of theranostics for true clinical application.

Systematic characterization of viral protein-host interactions yields invaluable information about viral invasion/evasion, diagnosis and therapeutic treatment of viral infections, and mechanisms of host biology. To facilitate these investigations, Labare's team released their panviral proteome collection that includes 2,035 ORF clones from 830 viral genes in the Gateway® recombination cloning system [7]. The researchers demonstrated several uses for this viral gene collection such as highly efficient viral protein production *in vitro*, global identification of host targets for the rubella virus using Nucleic Acid Programmable Protein Arrays (NAPPA) containing 10,000 full-length human proteins, and detection of host serological responses using micro-fluidic multiplexed immunoassays. This study illustrates a systemic utilization of viral ORFs, high-throughput cloning, and proteomic technologies to elucidate host-viral protein interactions. These available plas-

mid resources add tremendous value to the research community pursuing viral functional studies [7].

In recent years, disease biomarkers research has revealed a number of candidates to explore the mechanisms, underlying patient-specific variability in treatment response and efficacy. Although important first steps have been established, these studies would benefit from additional functional studies to determine underlying molecular mechanisms and thus, clinical utility of these biomarkers. In a separate investigation, a team at John Hopkins identified a set of blood-circulating glycoproteins that can differentiate human immunodeficiency virus (HIV) elite suppressors (ES) from healthy individuals and those with highly active anti-retroviral therapy (HAART) or AIDS [8]. The ES group comprises a very rare form in HIV+ individuals who can suppress viremia without HAART. Bioinformatic analyses revealed a strong correlation between inflammation and changes in protein presentation. Although inflammation-induced glycoprotein differences can be used to distinguish ES and HAART, there appear to be other triggers for inflammation and immune activation between natural and treatment-related viral suppression. Clarifying these unique molecular signatures should improve the design and development of improved clinical strategies for enhancing host resistance against HIV-1. In another study, through the comprehensive proteomics study, the investigator identified a mitochondrial protein that participated in DNA repair and exhibited the responsibility to the doxorubicin resistance in ovarian cancer [9]. Zhao et al. also indicated that miR-194 can act as a tumor suppressor in the colorectal carcinogenesis *via* targeting PDK1/AKT2/XIAP pathway by investigating it biological effects and mechanisms with a relatively limited samples cohort, and potentially, it could be a new diagnostic or prognostic marker in colorectal cancer [10]. Biomarker discovery is extremely important for the development of personalized medicine. However, we have learned that many reported biomarkers represent "false discoveries", as the subsequent validation studies may reduce the originally highly promising sensitivities and specificities to levels that are not clinically useful. Authors' next step will determine whether the findings of these informative biomarkers will be refined and validated to a degree that verified their clinical applicability, or will follow the fate of a myriad of biomarkers that either were false discoveries or were put on the shelf for lack of clinical value.

In theranostics studies, approaches based on RNA interference (i.e., small inhibitory RNA or siRNA) have gained much traction due to the virtually unlimited option to silence just about any gene [11]. A critical factor limiting their successful application *in vivo* is the lack of dynamic delivery systems capable of maneuvering biological barriers to reach target organs or tissues [12, 13]. To address these challenges, Shen group has developed a multi-component system for delivery of siRNA therapeutics, with each component designed to perform one or more specialized functions in negotiating the biological barriers [14]. As a proof-of-concept demonstration, the researchers delivered these multi-component systems loaded with siRNA targeting an essential oncogene to tumor cells. The delivery system with its siRNA payload accumulated at tumor sites and effectively suppressed tumor gene expression. These developments in systemic delivery of siRNA therapeutics underscore a great potential for broad applications both in basic research and in the clinic.

In contrast to the "one-size-fits-all" practices of the past, personalized medicine has emerged to include new designs for individualized drug therapy based on patient-specific characteristics and responses. The field of theranostics aims to promote safer and more efficacious pharmacotherapies that prescribe to patients the correct drug at the appropriate dosage. Success depends on multidisciplinary efforts, combined to expedite our understanding of host responses to "customized" theranostic agents and formulating individualized therapies.

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