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The grand challenge for integrative and regenerative pharmacology

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More robust identification of putative molecular targets for the development of novel therapeutics is a logical outcome of the post-genomic age of molecular medicine. Undoubtedly the concept of personalized medicine is becoming a reality (Hamburg and Collins, 2010), and in this scenario, the pharmacological sciences are ideally positioned to have a huge impact on the continued development of this field; specifically as it relates to the advent of mechanism-based, personalized therapeutics. In fact, the incredible rate of technology development and the parallel increase in our capacity to harness and apply the inordinate amount of information generated in the wake of these advancements creates tremendous challenges for our field, but also, enormous translational research opportunities.

The purpose of this article is to briefly review the Grand Challenge for Integrative and Regenerative Pharmacology, and to highlight how meeting the challenge will ensure our active participation in this exciting, and quite frankly unprecedented era of translational scientific endeavor. The Grand Challenge is codified below in general terms, but without question it will require a multi/interdisciplinary collaborative effort, on a global basis, to be successful. Furthermore, it is clear that each of the three aspects of this Grand Challenge could themselves be the subject of an entire review article. Herein we provide only a general conceptual framework to familiarize the interested reader with the overall topic.

The Grand Challenge for Integrative and Regenerative Pharmacology is three-fold:

1. To utilize Integrative Pharmacology (studies ranging from *in vivo* whole animal pharmacology/toxicology to complex *in vitro* and *ex vivo* systems) to obtain improved insight into *relevant mechanisms* of end organ/tissue dysfunction (i.e., target validation) as well as mechanisms of tissue regeneration, repair, and replacement.
2. To utilize cutting edge drug delivery technologies to improve localized delivery of therapeutic drug concentrations/effects, and furthermore, *enhance specificity* with respect to the cellular and subcellular targets/compartments of interest.
3. To leverage both 1 and 2 to create a new generation of therapies for improved symptomatic treatment of disease (i.e., fewer side/off-target effects due to improved MOA, enhanced localization, and cellular/subcellular specificity), and moreover, development of transformational *curative therapies* through the establishment of the principles of regenerative pharmacology.

UTILIZATION OF INTEGRATIVE PHARMACOLOGY STRATEGIES

As noted in our mission statement, the purpose of this Specialty Journal is to emphasize the importance of complex systems and whole animal research for the discovery of novel mechanisms of action and novel therapeutic entities leading to the discovery and development of new treatments for human disease. Implicit in this approach is the necessity to coordinate information obtained in complex *in vitro* and *ex vivo* systems with data obtained on rodent and large animal models that recapitulate relevant aspects of the corresponding human clinical conditions. Such an endeavor is intrinsically multidisciplinary, and pharmacologists will need to reach out to their colleagues in systems biology, bioinformatics, mathematics, engineering, etc., to be successful. As recently pointed out by Dr. Michael Rogers at NIGMS:

> "At this time, NIGMS has a substantial grant investment in pharmacology and in systems biology, but we have not seen a great deal of activity integrating pharmacology with systems biology to benefit drug discovery and the understanding of drug action." (https://loop.nigms.nih.gov/index.php/2009/09/09/a-new-frontier-for-therapeutics-integrating-pharmacology-and-systems-biology/).

In this regard, NIGMS has recently sponsored workshops to increase awareness of this critical effort, and to promote the required scientific interactions/collaborations. Further details about this important effort are available in a recent publication (Berg et al., 2010). The complexities of the "Integrative" or "Systems" pharmacology process are well beyond the focused nature of this brief report but have been elegantly addressed in another recent publication (Dollery, 2010). Importantly, the parallel development of novel training programs for preparing the next generation of researchers to participate in this aspect of the Grand Challenge has also recently been described (Sobie et al., 2010).

Without question, utilization of the resources and infrastructure resulting from this enormous effort represents an important tool with which to address this aspect of the Grand Challenge. Certainly, this collaborative approach falls well within the scope of Integrative and Regenerative Pharmacology. Encouraging examples of how a systems approach (i.e., multiscale analysis and mathematical modeling) may contribute to the development of novel therapeutics can be found with respect to recently published mathematical models of integrated calcium homeostasis (Peterson and Riggs, 2010), as well as with respect to the cardiac physiome project (Bassingthwaighte et al., 2009). Applications even more specific to Integrative Pharmacology have also recently been reviewed (Hendriks, 2010); where the importance of analysis of functional pathway pharmacology has been emphasized. That is, the development of computational models

that can account for the complexity of signal transduction networks. The rationale for this latter approach is that improved target validation (and improved clinical translation of preclinical results) should take into account both upstream and downstream pathway events, as well as the impact of the disease process, *per se*, on the pharmacological target of interest. The implications of this "systems" approach to Integrative and Regenerative Pharmacology are straightforward.

IMPROVED UTILITY AND ENHANCED SPECIFICITY OF THERAPEUTIC DRUG DELIVERY SYSTEMS

Another aspect of the Grand Challenge is the application of drug delivery technologies. Development and implementation of these cutting edge technologies clearly requires multi/interdisciplinary collaboration. Not surprisingly, modern drug delivery systems derive from technologies developed at the boundaries of nanotechnology, materials science, chemistry, and engineering. In this regard, a systematic and comprehensive review of modern drug delivery systems would be problematic even in a lengthy report dedicated only to that subject, in large part because these systems comprise a wide array of mostly application-specific technologies. Notwithstanding this, the goal of all of these technologies is to overcome a common set of barriers that limit the effectiveness of traditional pharmacotherapy, and moreover, extend the realm of deliverable therapeutic agents to a wider array of compounds, as well as gene therapies. The first of these barriers is the issue of vascular extravasation (Fukumura et al., 2010). That is, ensuring that the drug/compound/gene of interest leaves the systemic circulation to enter the tissue(s) of interest. Of course, drug delivery systems that utilize transdermal, injection, or direct implantation routes are by definition less dependent on extravasation. However, once the compound/technology of interest has been delivered to the tissue of interest, there are still local diffusion barriers in the tissue, and then, there is still the issue of cellular and subcellular targeting specificity. All of these issues are currently being addressed by a diverse group of labs on a worldwide basis. There are clearly major implications of the availability of these technologies to the pursuit of Integrative and Regenerative Pharmacology, wherein they could be utilized not only to provide enhanced symptomatic relief of end organ disease/pathology, but to modulate cell and tissue formation and function as well. For example, the use of nanoparticles (both polymer and lipid based) to enhance delivery of both genes (Pack et al., 2005) and other difficult to formulate/deliver therapeutics, such as those used for the treatment of cancer (Drummond et al., 2009) have recently been described. Furthermore, nanocarriers can be modified in numerous ways to cater to both the therapeutic indication, as well as the environment in the tissue of interest (Torchilin, 2009).

DELIVERY OF IMPROVED SYMPTOMATIC TREATMENTS AND TRANSFORMATIVE CURATIVE THERAPIES

The ultimate goal of Integrative and Regenerative Pharmacology is improved therapies for human disease. The last aspect of the Grand Challenge therefore is to optimize the alignment of Integrative and Regenerative Pharmacology with modern drug delivery technologies and systems pharmacology approaches. This will surely require a paradigm shift in the way that integrative pharmacologists think about developing novel therapies; specifically, a shift toward vastly improved symptomatic treatment of disease, and moreover, to the development of truly curative pharmacotherapies. For example, when there is sufficient viable tissue remaining, many new pharmacological strategies that leverage the newest developments in systems pharmacology and drug delivery systems can be envisioned for the improved treatment of disease/pathology, including Regenerative Pharmacology. However, when there is a paucity of viable tissue, or none at all, traditional pharmacotherapy will not suffice, and other approaches, such as tissue engineering and advanced regenerative medicine technologies (also under the auspices of Regenerative Pharmacology) will need to be implemented.

In summary, as with all of the medical sciences, there are many challenges ahead in Integrative and Regenerative Pharmacology. Nonetheless, it is time for a seismic move in thinking from developing drugs whose primary purpose is to treat symptoms (i.e., palliative) to developing drugs whose goal is to cure disease. This journal seems an ideal venue for outlining the possibilities, describing the journey, and publishing the results. The Integrative and Regenerative Pharmacology specialty journal hopes to keeps its finger on the pulse of the achievement of these worthy goals.

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