The need for a new search landscape for excipients with desirable *in vivo* properties.

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Editorial

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A relatively small number of excipient class molecules has the ability to drive the formulation of a theoretically infinite number of vastly structurally and functionally different APIs. This is true even with the advent of newer protein or gene drugs, where different permutations and combination of similar lipidic and/or polymeric backbone excipient molecules can ferry the (protein) API to the required site in the body and/or ensure (gene) expression. History teaches us that systems which can output a large quantity of information or achieve a large number of objectives with as small a number of constituents or blocks; or as small a toolkit; is usually evolutionarily successful. Note the evolution of DNA which can output a large amount of information with only four nucleotides in various permutations and combinations; or the eventual hegemony of a given language that can output a large number of words/meanings from a sparse 26 letters (as in the English language) of the alphabet in various permutations and combinations; as opposed to a pictorial based language. Only 92 natural elements; whose exquisitely similar fundamental characteristics nevertheless manifest as being sufficiently progressively diverse (rows) and sufficiently progressively similar (columns), can form an infinite variety of compounds when arranged or combined in various permutations and combinations. Only 10 octaves are required to produce the rich symphony of countless musical notes, medleys and compositions; even given the limited range of audible human hearing.

Might not then, the search for new excipients be more productive, and the results more applicable; if it were focussed on templating and expanding the class range of already existing excipients; rather than a heuristic trial and error testing of random molecules? This does appear to be the case historically; as well as being true of the current work in progress, where new excipients are largely structural expansions or modifications of existing excipients or food products. Such an innovative trajectory; by analogy to the 'less-is-more' examples earlier, has served well in the formulation of structurally and functionally diverse APIs; and there is no *a priori* reason to believe that it will not continue to perform successfully to formulate the increasingly complex API molecules of the future. Continuous progressive excipient expansion delivers an even larger permutation and combination landscape toolkit to work with. This process can be made even more efficient, and perhaps largely autonomous, with the advent of machine learning and Artificial Intelligence.

On the other hand, the Kuhnian critique of science as being an objective linear progression toward the

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truth, has relevance in terms of arguing that an ever-increasing toolkit expansion may be untenable; and may eventually plateau in terms of applicability, usability and formulation success; especially as they related to *in vivo* situations. There may be a reason why there are only 92 elements; and no more. There may be a reason why there are only 4 nucleotides; and no more. The Aristotelian geocentric model could only be defended up to the point of invoking Ptolemaic epicycles; but not beyond. At some point, the paradigm becomes indefensible. Could it be then, that excipient innovation needs to break with templating and expanding the current toolkit and look beyond the proverbial Periodic table's 'sea of instability' to find 'islands of stability'? In this context, perhaps the *ex vivo* excipient kit may well withstand progressive expansion, but new hunting paradigms may be required to achieve satisfactory excipient in vivo functionality.

How may this be achieved? We are long past the point where regulatory agencies anachronistic positions on what constitutes an excipient, and what does not, realistically no longer matter. The excipients of today and tomorrow, will need to (and do) modulate, cell signaling pathways; or to possess biopharmaceutical properties conducive to drug efficacy; whether the regulatory agencies like it or not; classifies them as such or not; or includes them as part of the drug delivery system to dodge the issue. We are past the point where excipients are – or can be - designed solely based on structure or physico-chemical properties, without regard to their *in vivo* functionality.

A suitable point to start exploring different landscapes would be to identify what the limitations of currently used excipients are; and are likely to be; in the context of their *in vivo* properties *viz*. that of ensuring bioavailability and decreasing the first-pass effect, maintaining drug stability and bloodstream persistence, (efficient and selective) cellular and organelle delivery and expression, decreasing immune rejection and reducing off-target effects. As always, nature should serve as our teacher. It then becomes a matter of observing and identifying which *in vivo* natural species/entities/cells/proteins... are good at accomplishing each of these aforementioned limitations. Subsequent research will provide the answers as to why these natural species are good at this. Then it becomes a matter of methodology. Methodological plagiarism from Nature will allow us to impute suitable molecules/ entities/ species/ cells/proteins.... with chosen desirable qualities. Note that none of these imputed qualities is devoid of pharmaceutical effect. Another avenue of exploration would be to identify populations that have some of these desired properties, for example, longevity, hypo or hyper immune systems, cytochrome P450 polymorphisms etc., and figure out a way to harness the mechanisms responsible into new excipients with the desired *in vivo* properties. Nature's inventiveness over a long period of evolution should render heuristic trial and error testing of random molecules unnecessary.

The rapid expansion of intricate mechanistic knowledge of druggable targets, and the computational design of drugs to engage those targets, has pushed existing excipients to the limit of their *in vivo* applicability. The most recent exercise, the empirical choice of the lipid constituents in the mRNA vaccines had fortuitously been under iterative development since the 1990s; the next time around, there may not be suitable excipients available. The culinary repertoire of excipients must not only impart new taste to old recipes, but must be able to create new recipes. If we continue along a path of mixing and matching existing excipients, or even new excipients that are templates of the existing ones, we may well end up with a situation where there may be drugs begging for excipients, and/or we run out of time.