Negative results in bio-medicine are urgently needed

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The development of statistical models and blind studies in medicine has changed our view of patient management. Evidence Based Medicine data now provide guidelines for treatment modalities. Meta-analytical studies performed on large populations have consolidated this trend. Are all these factors enough to promote further development in modern biomedical science? It seems not. In bio-medicine, analysis of negative results is valuable and stimulates the development of new methods and techniques.

Why are so little negative data published in bio-medical journals? Probably one reason is that Editors believe only positive data can stimulate the scientific and medical community. Secondly, Editors probably believe that papers containing positive results are more attractive for potential Readers, and this will result in a rising Impact Factor. This means that journals are mainly focused on positive and stimulating papers. Is it important? I think it is. It is not only important, but also dangerous and leads to much misunderstanding. Many papers on new interesting methods are published due to the positive results presented by Authors. Usually, many of these excellent and promising studies and therapies cannot be replicated by other teams and related research cannot be continued. Yet these papers are still included in bio-medical data bases. This confuses the next generations of researchers and doctors. Which paper contains really positive results? Which article contains results that are wishful thinking, usually published under pressure from many Editorial Boards who have adopted this kind of policy.

The good, or rather bad example of such wishful thinking is a paper published by Sakamoto, Schwarze, and Kyripanou entitled Anoikis disruption of focal adhesion-akt signaling impairs renal cell carcinoma.1 The Authors showed that doxazosin resulted in anoikis by disruption of focal adhesion-akt signaling in in vitro renal cell carcinoma cells. Doxazosin had been previously shown to influence apoptosis (or anoikis) in human prostatic cell lines. This substance was tested in in vitro prostate cells over many years, but no clinical (apoptotic) effect was found.2,3,4 Dear Reader, please try to find an answer and check it out for yourself. You have a lot of papers to choose from. You could start from 1998! The issue of the apoptotic influence of doxazosin on the prostate gland seems to be utterly exhausted. Clinical practice has shown that a proapoptotic in vitro influence of doxazosin on prostate cells was meaningless. If you take a look at prostate cancer treatment, you can come to the same conclusion; so far no effect has been observed.3,4 Doxazosin is a very good drug for patients with benign prostatic hyperplasia. It decreases muscle tension and thus increases urinary flow, but the mechanism of action is not related to apoptosis.

Will doxazosin have an apoptotic effect in clinical conditions on renal cell cancer as proposed by Sakamoto and colleagues?5 It is hard to believe. It is a known fact that prostate and kidney malignancies have cancer stem cells which are insensitive to any natural and prepared epigenetic influences both in vitro and in vivo, including doxazosin.5,6 Have the Authors of this paper taken this fact into consideration? Of course, we can carry on publishing ad infinitum such enthusiastic papers containing only well documented successes; but what will this achieve?

On the other hand, we have a really good example of a paper prepared by Nuininga, Koens, and co-workers entitled Urethral Reconstruction of Critical Defects in Rabbits using Molecularly-Defined Tubular Type I Collagen Biomatrices: Key Issues in Growth Factor Addition and published by Tissue Engineering.7 This paper is interesting for two main reasons. The first reason is purely empirical and scientific, and the second is related to the potential applicability of this study. The Authors presented two collagen type I matrices; one (COLX) without growth factors was compared to improved matrix enriched with VEGF, FGF-2 and EGF (COLX-Hep-GH), so-called smart scaffold for tissue engineering. I think that the most striking aspect of this study is the differences between histology and functional in vivo results. COLX-Hep-GH substantially improved molecular features of healing but failed to be superior in functional outcome (i.e. narrowed urethras, urethras with diverticula, and one fistula) over the unmodified matrix. This is the most important message from this study and my suggestion is to pay much more attention to this phenomenon. I would emphasize the negative influence of this study, in an intensive and intensively prefabricated COLX-Hep-GH matrix. This is the clue to this paper. The negative effect of this over-treatment, as we can call it, is the most important issue. Authors have presented the problem of how difficult it is to prepare a good dose of growth factors for regeneration. The negative results of this work have a positive value. We know that such a simple, unmodified, pure COLX scaffold still has unsatisfactory properties and has to be improved. Such an experiment has the potential to influence the scientific community, providing proof that acellular scaffolds are probably not inferior to some of the popular and desired scaffolds pre-loaded with growth factors. So negative results are also important. Negative and positive (or successful) results provide us with the framework of our experimental work. Clinicians are obliged to search for and find a real reason for treatment failure or success. We have to encourage Authors to submit well prepared, quality bio-medical manuscripts which also contain negative results, and Editors have to encourage these Authors to publish them.

References