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Editorial

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The Problems with the Cells Based Assays

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An important part of the classical drug discovery paradigm is the cell based assay. Medicinal chemists, after identification of the molecular target such as enzyme or receptor are quite efficient with the design and synthesis of a potential inhibitor or receptor antagonist. If crystal structure of the target proteins is available, computer modeling accelerated the overall process substantially. Also the combinatorial libraries could supply a large number of interesting new chemical structures. In a relative short time, medicinal chemistry could create a large number of the potent inhibitors or receptor antagonists. It is impossible to test all of them in an expansive and time consuming animal model of disease. Therefore, medicinal chemistry relays on indirect selection assays, mainly the cell-based and/or tissue-based assays. However, there are many issues concerning the question of how much such assays are relevant to the real human pathological conditions. This new journal (Cell Biology: Research & Therapy) address these issues and is also a good addition to the existing communication platforms.

Very instructive is experience coming from our research concerning the search for an osteoarthritis drug performed during 1994-1996 [1,2]. At this time, the identity of the enzyme responsible for pathological cleavage site in human aggrecan was not known. Today, it seems the HtrA1 serine protease is responsible for the generation of aggrecan fragments containing the VQTV (356) neoepitope. This peptide fragment is significantly more abundant in osteoarthritic cartilage compared with cartilage from healthy joints [3,4].

At the beginning of our search we had in hand an immortalized human chondrocytes assay from Goldring et al. laboratory [5], bovine and occasionally human articular cartilage explant [1,2]. An immortalized human chondrocytes synthesized some elements of extra cellular matrix and degradation of that could be seen under influence of IL-1 [5]. We did include such cell assay in our discovery pathway and in few weeks identified several new compounds able to give significant chondroprotection to this system. After lot of discussion and with a high degree of skepticism, we introduced these compounds to the guinea pigs osteoarthritis model and noticed a strong acceleration of the disease and almost complete degradation of articular cartilage. Clearly, this model assay is not predictive for an *in vivo* situation. The cartilage explant models of matrix degradation were also problematic at some points. While the IL-1 induces degradation in bovine articular cartilage explants, it was not affecting human articular cartilage explant [2]. However, after the addition of plasminogen, in the concentration found in synovial fluid, a significant degradation of matrix was observed [2]. We regard this model as one which resembles in the higher degree the real pathological situation *in vivo*. Matrix metalloproteinase's (MMP's) are not one of the main players but they contribute to the matrix degradation during the progress of osteoarthritis. We have designed a set of new inhibitors for these enzymes and they slow down the cartilage degradation in last model, the bovine articular cartilage explants with the addition of plasminogen at a physiologically relevant concentration. Several of these compounds show significant activity in slowing down cartilage degradation in the guinea pig model of osteoarthritis when injected directly to the synovial fluid [6].

In summary, we need to be very skeptical about our data coming from the cell/tissue based assays and keep in mind that they are so much relevant to real physiological *in vivo* situation as much as our model is similar to that.

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