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Selective Vitamin D Receptor Modulators (SVIMS) as Potential Adjuvant Therapeutic Agents

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Vitamin D3 (cholecalciferol, D3) is one of the most important forms of vitamin D in human health [1-4]. There are two sources for human beings to obtain vitamin D3. The first source is the conversion of 7-dehydrocholesterol (7-DHC) in the skin to pre-vitamin D3 by UVB irradiation from the sunlight, followed by thermal isomerization to produce vitamin D3 (Figure 1) [5]. This is a tightly regulated process by the human body, and it is impossible to result in vitamin D3 overdose. The second source is through diet supplements. Human body cannot regulate this source of intake well, and vitamin D3 overdose and subsequent toxicity could occur. Interestingly, vitamin D3 itself is not the biologically active form. It must be first hydroxylated at the C25 position in the liver to produce 25-hydroxyvitamin D3 (25(OH)D3), followed by a second hydroxylation at the C1 position in the kidney or by monocyte-macrophages in the immune system to produce the biologically active form 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D3$) (Figure 1). $1,25(OH)_2D3$ binds to the Vitamin D Receptor (VDR) which ultimately lead to its various biological functions (Figure 1).

Apart from their classical action of regulating bone health and calcium homeostasis, there are accumulating evidence in the literature suggesting that vitamin D3 also have non-classical actions including strong inhibition of cell proliferation, promotion of cell differentiation, and suppression of inflammation responses [5-8]. However, the use of $1,25(OH)_2D3$ at its effective dose is often limited by its severe hypercalcemic side effect in which calcium concentrations in serum reaches dangerously high levels (>10.5 mg/dL) [9]. The high concentration of circulating calcium could deposit in software tissues such as heart, liver, and kidney, and could ultimately result in tissue calcifications [9].

There have been tremendous efforts in both industry and academia to develop new vitamin D3 analogs that can retain the beneficial effects but have minimal or absence of the undesired hypercalcemic side effects, for a variety of potential indications such as cancer and inflammation [8,10-16]. Many potent vitamin D receptor ligands have been discovered or synthesized, and several made to clinical trials (examples are shown in Figure 2).While Zemplar is an approved drug used to treat secondary hyperparathyroidism (over activity of the parathyroid gland) in people with chronic kidney failure, at present, however, there are no FDA approved vitamin D3 analogs that can be used safely to effectively treat cancer or inflammation disorders (Figure 2).

Traditionally most of the new vitamin D3 analogs reported in the literature can be classified as "super VDR agonists", that is, a compound has significantly higher affinity in binding to the VDR than its natural ligand $1,25(OH)_2D3$. The rationale is that just a tiny amount of the compound will be required to activate the VDR to produce the desired biological function, without reaching the higher concentration which may lead to hypercalcemia [8]. This is a valid approach, but it also has its limitations. Another approach recently proposed by researchers including our labs is based on the hypothesis that desired tissue-selectivity, rather than the absolute binding affinity to the VDR, hold the key to develop new generations of clinically useful vitamin D3 analogs. In fact, VDR belongs to nuclear receptor families, and it is well known that many therapeutically useful ligands for some of these nuclear receptors have excellent tissue-selectivity. Two examples are Selective Androgen Receptor Modulators (SARMs) [17-19] and Selective Estrogen Modulators (SERMs) [20-23]. Therefore, similar to SARMs and SERMs, it should be possible to develop Selective Vitamin D Receptor Modulators (SVIMs). While there are many types of potential tissue-selectivity can be defined for different therapeutic indications, one promising tissue-selectivity is the selective VDR activation in immune cells over in intestine cells. VDR activation in the immune cells is responsible for its strong suppression of inflammation responses, while VDR activation in the intestine cells is responsible for the undesired hypercalcemic side effects. If a SVIM selectively activates the VDR in the immune cells over the intestine cells, such an agent will likely to be very useful in treating a variety of immune diseases such as arthritis for which more effective therapies are urgently needed given the increasing lifespan of populations, especially in the developed countries. It is also helpful to realize that for some diseases such as cancer and chronic inflammations, it may not be realistic to use a single agent for very effective treatment; therefore, a rationally designed drug combination treatment strategy in which a SVIM serving as an adjuvant agent adding to the standard treatment may provide the best benefits for patients.

Currently there are several hurdles researchers need to overcome in order to facilitate the development of clinically useful SVIMs. First, we need a clear understanding of molecular mechanisms leading to the desired tissue-selectivity. Several potential reasons can lead to the tissue-selectivity, including VDR polymorphism, differential distribution/functions of VDR in different tissues, alternative targets for SVIMs, different downstream responses from VDR, etc. Availability for such information will be tremendously helpful in this drug discovery process. Second, relatively easy and reliable *in vitro* assay methods that can reasonably predict the *in vivo* responses for SVIMs will be very useful. Calcium absorption in the intestines and the immune functions are extremely complicated process. While *in vivo* experiments will be the best predictor, they may not be very practical in screening a large number of potential SVIMs. Developing reliable *in vitro* assays will facilitate this area of research substantially. In summary, while there are indeed significant challenges faced by developing clinically useful SVIMs, it also provides rich opportunities to advance the science for this area of research.

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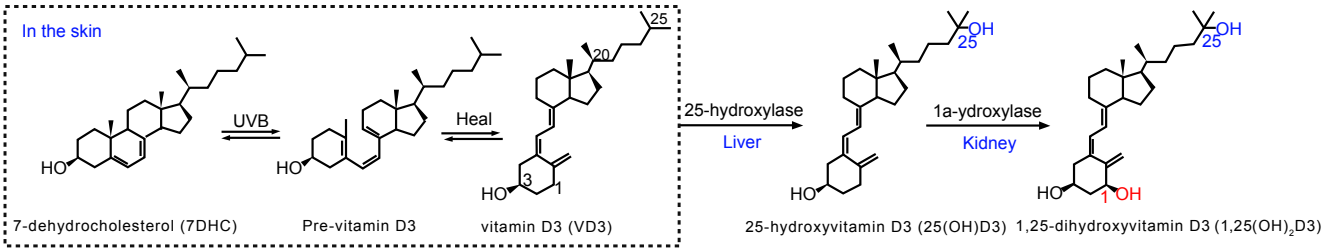

Figure 1: Generation of vitamin D3 from 7-DHC in the skin and the activation of vitamin D3 to its biologically active form 1,25(OH)$_2$D3 in the human body.

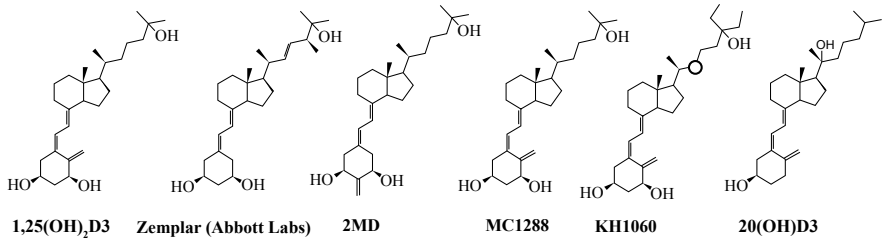

Figure 2: Examples of existing potent VDR ligands and their structural comparison to the VDR native ligand, 1,25(OH)$_2$D3.

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