
CGEN-15001: *EXAMPLE OF “DISCOVERY ON DEMAND”*

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This presentation aims to provide you with some insight into our discovery on demand capabilities. This will be done by using as an example one of our most recent discoveries - CGEN-15001, which was the subject of a press release by the company earlier this month.

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First, a very brief introduction to the B7/CD28 Protein Family. In general, all proteins either remain within the cell where they were expressed, or are secreted into the bloodstream – such as insulin – or are attached to the cell surface. The B7/CD28 family of proteins belongs to this latter type. They are attached to the surface of cells, primarily cells of the immune system. B7/CD28 proteins are known to play a critical role in the defense of the body against disease. Essentially, they modulate the immune system in order to protect the body’s “self” cells, and to destroy “non-self” cells, such as tissue cells introduced by organ transplant. In addition, some of these proteins are found on cancer cells and apparently are used by the tumor to block the immune system from attacking it. Due to this involvement in immune response, these proteins play a role in many pathological conditions including autoimmune diseases where the immune system turns against ‘self’ cells, such as in multiple sclerosis, diabetes and cancer. This is the reason why this family of proteins is of very substantial interest to the pharmaceutical industry and led to our decision to utilize our “discovery on demand” capabilities to attempt to discover new B7/CD28 protein family members.

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For our initial efforts on this program, we decided to focus on that subgroup of B7/CD28 proteins that are expressed specifically on cancer cells, since such proteins would have potential therapeutic usage not only in autoimmune diseases and transplant rejections, but also in cancer.

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Existing approaches for discovery of B7/CD28 proteins in general involve “traditional” bioinformatics combined with experimental approaches. Family members discovered in the last few years were largely found by sequence homology analysis and experimental verification. However, current attempts at discovery of additional novel members are much more challenging, since as with all traditional discovery approaches, the easier ones – the so-called “low hanging fruit” are found first, and then it gets more and more difficult. Those family members that are still believed to be left to discover probably have very low sequence homology, otherwise they would have already been discovered by the

traditional methods that have been employed by researchers in the field. Also, available public computational tools are largely insensitive to key known B7 characteristics, and therefore are unlikely to aid in the identification of those B7 members that have low sequence homology.

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How did Compugen discover new family members? And, specifically, how were we able to identify a novel B7/CD28 family member? First we employed our LEADS infrastructure platform, which, in addition to other capabilities, predicts the human proteome. Even though the LEADS infrastructure platform is one of Compugen's earliest platforms, it is continuously updated with improved algorithms and new data, and remains a core competitive advantage for our protein and certain other discovery capabilities.

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Use of the LEADS platform provided us with the starting point for our program – an in silico proteome, consisting of, what we believe to be, all the possible human proteins that could exist. Since as previously mentioned, all B7/CD28 family members are membrane proteins, we next applied tools based upon machine learning and additional algorithms to identify from all the predicted human proteome, those proteins that are predicted to be membrane proteins.

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Next, we applied algorithms developed by our scientists to identify and rank characteristics of known B7/CD28 family members, based on the protein family's genomic information and protein domains. These algorithms, based on extensive research by Compugen during earlier years, are a key component of our protein family discovery platform, a platform which has not been formally announced since it is still under development, but has been used very successfully in this activity. So at this stage we applied the B7/CD28 characteristics algorithms that we developed, to our prediction of all human membrane proteins, and the result was our prediction of probable B7/CD28 family member proteins.

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Next we screened probable B7/CD28 family member proteins for their expression on cancer cells. This was done through our second infrastructure computational platform that allows the analysis and prediction of expression of various predicted proteins in healthy and diseased conditions. The result of this step was our prediction of putative targets for cancer treatment.

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These in silico predicted family members were then prioritized for experimental validation and analysis, based on their relative scores to be membrane proteins, to be members of the B7/CD28 family, and to have potential to serve as cancer targets. This process resulted in the selection of CGEN-15001T for experimental validation.

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On this slide, in the diagram on the right, the orange bars represent the cell membrane, and the figure resembling a twisted rope represents a membrane protein, such as CGEN 15001T, attached to the membrane. Also as shown, a piece of CGEN 15001T is outside the cell, and this is termed the extracellular domain. It is this extracellular domain that can serve as a target for an antibody totally specific to that extracellular domain, that will attach to it, and then by various mechanisms, attempt to kill the cancer cell.

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With respect to serving as a drug target for oncology, on this slide we see how the transcript for CGEN-15001T is very strongly differentially expressed in small cell lung cancer. Also, as we predicted, the respective recombinant protein was found to localize to the membrane of cells expressing it. These results are very encouraging, however they are very preliminary and therefore additional studies are now underway.

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These additional validation studies for use of CGEN-15001T as a drug target for monoclonal antibodies therapeutics in cancer are now on-going. Although CGEN 15001T is very promising as a drug target for cancer, as of now, the most exciting aspect of this discovery program is that we have created an additional novel therapeutic entity based on it – CGEN 15001 – for potential use in autoimmune diseases and transplant rejection, and which was the subject of a press release earlier this month.

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Before providing additional information regarding CGEN 15001, a few words about autoimmune diseases and transplant rejection. Sometimes, the immune system mistakenly attacks its own “self molecules” resulting in autoimmune diseases such as Multiple Sclerosis, Rheumatoid Arthritis, Diabetes Mellitus Type 1 or others. In other cases, such as transplantation, there is a need to “shut down” normal immune response to non-self molecules introduced by the transplant.

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The majority of approved drugs for both autoimmune disease and transplant rejections act by suppressing the entire immune system. A more targeted shut down approach, such as offered by CGEN-15001, would be more specific and therefore clearly advantageous over existing medications (for example it is likely to cause fewer side effects). Therefore, such a targeted shut down approach is a major area of therapeutic need and a key focus for many pharma and biotech companies.

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The new Compugen molecule is based on the extracellular portion of CGEN 15001T – as shown on this slide. It is a soluble protein that can act as the therapeutic agent itself. CGEN 15001 was predicted by Compugen to interfere with certain immune cell

processes, such as those occurring in autoimmune diseases as well as in transplant rejection.

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After producing CGEN 15001, we began the experimental validation of its therapeutic potential. We first tested the molecule *in vitro*. Our goal was to demonstrate that this molecule can inhibit the immune T cell response that occurs in autoimmune disease – such as MS and diabetes - when the body attacks its own self molecules. For this purpose we measured typical T cell responses: T cell proliferation, differentiation and cytokine secretion – processes known to occur in T cell modulation.

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Here are examples of the results. In the upper left graph we measured the T cell proliferation. The Y axis relates to an increased level of proliferation and the X axis relates to an increasing concentration of the molecule tested. As expected, adding a negative control molecule (represented by the red line), had no effect on the multiplication of T cells. As a positive control, we used a known B7 family member (represented by the green line), which resulted, as expected, in the reduction of cell proliferation as a function of its concentration. The blue line presents the results obtained for CGEN-15001, which showed, as we predicted, a similar reduction in cell proliferation.

In the lower right graph we measured the effect of CGEN-15001 on cytokine secretion from T cells. The Y axis relates to the level of cytokine secretion and the X axis relates to the various cytokines that were tested. As you can see, all of the red bars representing the negative control show high cytokine secretion – which is typically associated with T cell activation, while the blue and the green lines, the positive control and our CGEN-15001 soluble protein, respectively, as predicted, inhibited cytokine secretion from the activated T cells.

These promising results, and additional results from studies, not shown in this presentation, clearly indicate that the protein inhibits an immune T cell response, as we predicted.

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Our next step was to confirm the potential of this protein to serve as a therapeutic drug for various autoimmune disorders. We selected multiple sclerosis (MS) as the first disease model to evaluate this potential.

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The animal model we used represented relapsing-remitting MS disease. This disease is the most common form of MS; moreover, the clinical and pathological symptoms present in this well recognized animal model are similar to those in human disease. Our motivation to perform such a study was to determine whether our molecule could prevent relapses in MS, which is a major goal in the development of treatments. This is because MS relapses result in recurring attacks of clinical symptoms and lead to aggravation of existing symptoms and to the appearance of new ones.

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This graph demonstrates the results we observed with CGEN-15001 when it was administered before disease onset in this animal model. The Y axis relates to disease severity and the X axis relates to the number of days after disease induction. The colors of the graph are similar to what you have seen before, only now the positive control – the green line – is representing a different known active molecule. As you can see, the negative control – the red line - has no effect on the disease which starts at day 10 and peaks at about day 22. It is then remised, but as you can see additional disease relapses occur with time. Under these disease conditions, the animals of both the positive control and those that were administered with CGEN-15001, demonstrated a delay of disease onset (from day 10 to around day 15) and a significant decrease in disease severity.

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Additional exciting results have been achieved to date as shown on this slide. In this case, CGEN-15001 was administered in the presence of the disease (at day 20) – what is called a therapeutic mode of administration, as opposed to the preventive mode that was shown in the previous slide. The Y axis relates to disease severity and the X axis relates to the number of days after disease induction. As you can see, the negative control – the red line – as expected has no effect on the disease showing spontaneous relapses and remissions. However, the administration of CGEN-15001 completely abolished spontaneous relapses (essentially at day 50 and onwards). These animals are still under evaluation and I am very pleased to report that even now, about 2 months after the administration of CGEN-15001, the animals are still in full remission. These experiments provide strong evidence of the therapeutic effect of CGEN-15001 in MS diseased animal models and as such, indicate its likely relevance for use in human therapy.

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It is worth repeating what Professor Miller from Northwestern University, a leading expert in the field who supervised the studies said about our molecule. “The effect of this molecule is quite dramatic”. “It may prevent disease progression as efficiently as immune tolerance induction” and “these findings, together with those demonstrated in our earlier studies, are unique among the molecules targeting the B7 family of co-stimulatory molecules that have been published to date”. It is therefore not surprising that we are now seeing a very high level of interest in this molecule by numerous pharmaceutical companies.

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As mentioned earlier, the majority of FDA approved therapies in this general area focus primarily on global inhibition of immune inflammatory activity. In comparison, CGEN-15001 is expected to be devoid of general immunosuppressive effects and may therefore have a significantly decreased risk of opportunistic infections occurring while treating the disease condition.

Also, based on and additional results from studies, not shown in this presentation, it appears that CGEN-15001 has the unique ability to inhibit the production of undesired

immune responses while promoting preferred immune responses. This is a unique feature among molecules targeting B7/CD28 molecules, and if further confirmed, would represent a major medical and commercial advantage.

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In summary, I hope I have demonstrated by this specific application, Compugen's "Discovery-on-Demand" approach, which is capable of discoveries in fields of substantial industry interest, specifically those where traditional discovery approaches are not succeeding. In this specific case, our efforts to date have resulted in the entirely *in silico* prediction of two previously unknown molecular entities from the same core discovery – one being the entire molecule that was discovered, and the other based on a portion of such molecule - with applications in many important therapeutic areas, including oncology, autoimmune disorders and transplant rejection..

Looking to the future, the protein family discovery platform used in this program, which as previously mentioned is still in development, may be applicable to additional protein families of significant clinical and industry interest and thus adding to our capability in future "discovery on demand" collaborations. Furthermore, with our powerful infrastructure platforms such as LEADS and MED, and an additional Twelve announced validated discovery platforms, we are confident that Compugen has the capability to uniquely address discovery challenges across an extremely broad range of unmet needs in diagnosis and therapy.