A First-In-Class Small Molecule Type 2 Diabetes Therapeutic: Menin-MLL Inhibitor (iMen) - REVERSING DIABETES VIA RESTORING PANCREATIC ISLET MASS AND FUNCTION THROUGH BETA CELL REGENERATION

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OVERVIEW

Novapeutics LLC is a biopharmaceutical company spun-out from the University of Pennsylvania situated at the Pennovation Works campus. We are developing a menin-MLL (Mixed Leukemia Lineage Protein) inhibitor (menin-MLL inhibitor), a small molecule (iMen ~500 Dalton) that inhibits the menin and MLL interaction as an oral therapeutic for type 2 diabetes (T2D). This is achieved by restoring the insulin producing beta cells would especially be useful for treating advanced stage T2D patients, many of whom suffer from inadequate and non-responsive beta cells in the pancreatic islet. By regenerating beta cells would restore patients' endogenous ability to produce normoglycemic factors, such as insulin and amylin to properly manage the blood sugar level. Early stage T2D patients suffer from low insulin and/or may not respond effectively to insulin.

There are two common types of diabetes, Type 1 diabetes (T1D) and T2D. T2D is 20 times more prevalent in adults over the age of 18 years old than T1D. T1D is often hereditary and not preventable. T2D can also be hereditary, however usually is attributed to aging (over 40 years old) together with unhealthy diet and lack of exercise as major risk factors. It is estimated that at least a third of adults that are born after the year 2000 in the United States will inevitably develop T2D in their life time. Both types can lead to heart attack, stroke, nerve damage, kidney damage, and possible amputation of limbs. In T1D, it often affects children and young adults, and it can start suddenly. T1D occurs when the immune system mistakenly attacks the insulin-producing pancreatic beta cells. T2D starts when body is chronically inundated by the elevated blood sugar and insulin, and the body becomes seemingly irresponsive to insulin, and beta cells death increase due to this chronic stress. This steady decrease in the beta cells accelerates the T2D progression. However, early intervention with healthy diet and exercise could prevent or reverse the early onset of T2D. For the advanced diabetes, iMen would provide the possibility to reverse advanced T2D progression, and hopefully allowing healthy diet and exercise

to be effective once again. However, for T1D, iMen can only provide some relief by increasing beta cells, and the autoimmune part of T1D would have to be treated simultaneously.

Conventional treatments for T2D directly or indirectly (one step removed) influence the regulation of the blood glucose levels, which are modulated with significant fluctuations that leads to diabetes complications. These treatments include insulin replacement/secretion, insulin sensitization, hepatic glucose output reduction, delay of intestinal carbohydrate absorption, and incretin enhancement / replacement therapies, and blockade of glucose reabsorption in kidney (Sodium-glucose co-transporter 2-SGLT2-inhibitor**)**. Our therapeutics approach is to use a small molecule stimulate beta cell regeneration by inhibiting the Mixed Lineage Leukemia protein (MLL) from interacting with our target protein menin (a protein encoded by the *Men1* gene) to allow beta cells to regenerate. We would like to provide an oral therapeutic for the advanced T2D, to replace the injectables, such as insulin, exenatide, liraglutide, and pramlintide. An oral drug will increase patients' compliance for treatment, and with our beta cell mass restorative approach could potentially reverse diabetes even at their advanced stage.

IMPACT: SOCIAL AND ECONOMICS

According to the American Diabetes Association (ADA), an estimated 90%-95% of adults in the US with diabetes suffer from T2D. The prevalence of T2D is projected to grow in concert with obesity (2). This will lead to a rapid increase in the number of T2D patients to the advanced stages of the disease - on average constitutes 10-12 years of a patient's life. This continue dependence of insulin and injectables negatively impacts advance diabetics' day-to-day quality of life. In the year 2012, it was estimated that 29.1 million American adults (over the age of 18) suffer from this dreadful illness and the economic burden was estimated in 2013 to be $176 billion in the direct medical cost; while the indirect cost was around $69 billion dollars, due to reduced annual productivity loss per person (1). Alarmingly, the number of diabetics in the United States is projected to double by the year 2034 and its medical cost will nearly triple to $336 billion dollars (1). In 2013, 2.2 million advanced T2D patients were treated primarily by injecting insulin with a syringe or a pen more than once every day. Other injectables such as exenatide, liraglutide, and pramlintide are also used. With a 7% compound annual growth rate (CAGR) (3), the T2D population in the US will reach 67 million by 2025, with 7.3 million adult diabetics at the advanced stage.

Currently, only 73% of diabetes patients is estimated to take their medications as prescribed (4). Increased adherence to diabetes medication can reduce emergency room visits by 1 million and this could save the U.S. economy $8.3 billion each year. Globally, the impact of T2D is equally devastating. World Health Organization (WHO) published on April 2016 that 422

million adult (over age of 18) worldwide are diabetics in the year of 2014. In particular, in accordance to WHO classification the regions of Americas had 62 million adult diabetics and European region had around 64 million adult diabetics, when combined has 126 million adult diabetics in the Western countries. In less than a decade, the seven major markets for diabetes: U.S., France, Germany, Italy, Spain, UK, and Japan are expected to grow to $35B, driven by expansion of patient populations. In 2013, 18% of the direct medical cost is contributed to by prescription drugs for diabetes, translating to $31.7 billion per year and with an estimated number of 31 million adult patients, this translates to $1022 dollars spent per patient directly on therapeutics (5). Out of all the diabetes adult patients, 12% use insulin, 14% use a combination of insulin and oral medications, 58% use oral medications exclusively, and 16% use no medication at all (6). Advanced diabetics chronically use the injectables that are uncomfortable to deliver, costly, easy to under- and over- dose, and inconvenient to use. Novapeutics plans to replace injectables with our oral drug iMen to restore body's natural ability to normalize blood glucose and increase patients' compliance by reducing the dependence on the injectables. Therefore, when looking at the societal impact that is directly associated to the dollars and cents spent in healthcare, it is clear that diabetes is an epidemic that is in the urgent need for a disruptive solution.

NOVEL MECHANISM OF ACTION (MOA)

A hallmarks of T2D is hyperglycemia subsequent to inadequate numbers of functional pancreatic beta cells that results in insufficient insulin secretion. Research conducted by Professor Hua at the University of Pennsylvania (1, 7, 8) identified the nuclear scaffold protein menin as a novel diabetes therapeutic target, by severing the interaction between menin and MLL allows the beta cells to regenerate. This novel MOA was first discovered in the murine genetic experiment in both inducible model and acute elimination of menin. This proof of concept studies for the target menin in the animals was first published in the *Journal of Proceedings of the National Academy of Sciences* in 2010 (8). High-fat diet (HFD) increases body weight and induces metabolic syndrome and diabetes in mice (9, 10). *Men1* ablation in mice, which closely phenocopies human MEN1 syndrome (7, 11, 12), leads to reversal of pre-existing hyperglycemia in HFD-induced diabetes or diabetes of *db/db* obese mice. These experimental models for T2D (1, 8) validate menin and beta cell regeneration. In short, eliminating menin increases beta cell regeneration, beta cell number, and circulating insulin concentrations and subsequently reverses glucose intolerance in HFD-fed mice.

Our target menin protein that has up to 20 different binding partners and around 10 identified functions, iMen's MOA works by inhibiting the menin and MLL protein interaction with high selectivity. Menin has been suggested to be potentially a tumor predisposition gene in the endocrine system (13), therefore some may wonder if our MOA could be tumorigenic. This concern has been addressed by the work of a complete menin gene deletion in various genetic diabetes murine models without tumorigenesis while reversing diabetes via restoring pancreatic islet mass and function (1, 8). Furthermore, this very same MOA has also been implicated for treating blood cancer (14-16). For example, at least two pharmaceutical companies, Kura Oncology and Syndax Pharmaceuticals are already developing pre-clinical programs using iMen to treat acute leukemia. Albeit it is highly unlikely that our MOA could be a concern for tumorigenesis, any regenerative approach deserves to be paid close attention to which we would examine during the iMen drug development process. Most notably, iMen has also been under development as an anti-oncogenic agent for a novel leukemia therapeutic.

Menin interacts with several partners, including transcriptionally activating MLL histone methyltransferase, to upregulate cyclin-dependent kinase inhibitors (Cdk), $p18^{ink4c}$, and $p27^{cip1}$ (Figure 1) (17). Interrupting menin and MLL binding will eventually reverse this regenerative inhibition, thereby repressing expression of $p18^{ink4}$ and $p27^{cip1}$ and thus triggering beta cell regeneration. Our co-founder Professor Hua and colleagues had recently solved the menin-MLL complex crystal structure (18). This information allows us to use computational structure drug design approach to generate rationally designed novel iMen derivatives as drug candidate.

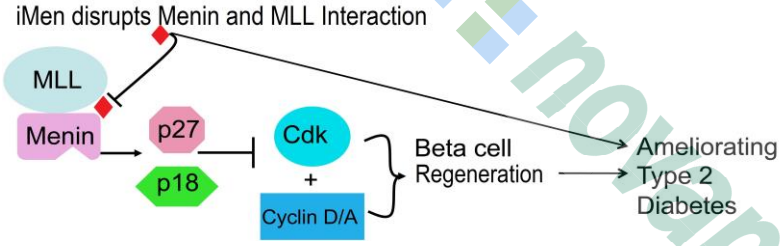


Fig 1: iMen Interrupts Menin-MLL interaction and allows beta cell regeneration. Inhibiting menin and MLL binding relieves regenerative inhibition, thereby repressing expression of $p18^{ink4}$ and $p27^{cip1}$, this allows Cdk and Cyclin D/A to promote cell cycle and thus triggering beta cell regeneration.

As shown here in Figure 2a and 2b (the normalized percent inhibition of iMen compounds on the Menin-MLL complex) all compounds were analyzed by Fluorescent Polarization (FP) assay, and then normalized using DMSO. In both Figure 2a and 2b, IC_{50} values for each compound were calculated for their percent of inhibition, which was derived from the mP values of each sample that results in the following IC_{50} as shown in Figure 2a: iMen201=12.5μM; iMen207=0.67μM, and iMen208=2.1μM; and in Figure 2b: iMen-327=1.5μM; iMen328=0.09μM; iMen329=3.20μM; iMen330=12.67μM; and iMen331=0.04μM. iMen compounds were created via using rational drug design approaches, such as analyzing menin's structure and its druggable pocket (18, 19) coupled with integrating public information available for our medicinal chemistry development. As to the methods for Figure 2a and 2b, we used our Fluorescence-Polarization (FP) assay designed specifically for iMen drug lead screening purpose and to detect and quantify their potency to interrupt menin-MLL bindings.

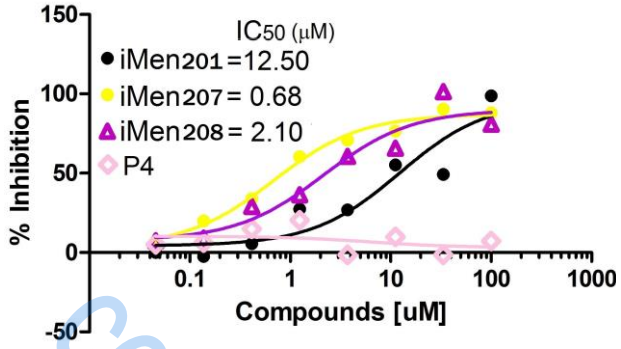


Fig 2a: Second Generation: iMen201, 207 and 208 compounds inhibit menin-MLL interaction as shown in Fluorescence-Polarization (FP) assay. (A) iMen201 (●), with IC_{50}=12.5μM. (B) iMen207 (●), with IC_{50}=0.68μM; (C) iMen208 (△), with IC_{50}=2.1μM; FP of menin with FITC-MLL, competed against iMen201, iMen207, or iMen208 compounds, or negative control p4 (◇), with the competition by a positive control peptide p17 (not shown) designated as 100% competition. Resulting in selecting the iMen207 (●) as a candidate for further development.

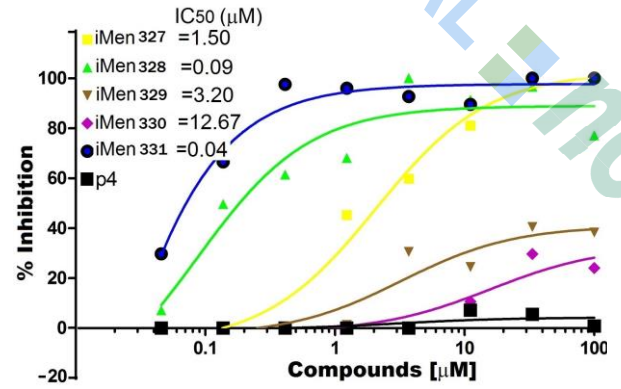


Fig 2b: Third Generation: iMen328 and iMen331 compounds are potent interrupters for the menin-MLL interaction as shown in Fluorescence-Polarization (FP) assay. (A) iMen327 (■), with IC_{50}=1.50μM. (B) iMen328 (▲), with IC_{50}=0.90μM; (C) iMen329 (▼), with IC_{50}=3.2μM; (D) iMen330 (◆), with IC_{50}=12.67μM; (E) iMen331 (●), with IC_{50}=0.04μM; FP of menin with FITC-MLL, competed against iMen327, iMen328, iMen329, iMen330, or iMen331 compounds or with the negative control p4 (■), with the competition by a positive control peptide p17 (not shown) designated as 100% competition. Resulting in selecting the iMen328 (▲) and iMen331 (●) as candidates for further development.

To do this, FITC-labeled RWRFPGTGRR peptide was used as a probe, purified from *E. coli*, based on the FP assay we developed. We verified the specificity of the FP assay by showing that the FITC-MLL binding to menin was competed away by the wild type MLL peptide (P17) as the top limit designated as the inhibition of 100%, but not by the mutant peptide (P4) as shown and designated as inhibition 0%. Using this FITC-MLL peptide as a probe we screened our designed and synthesized small molecules for their ability to inhibit menin and MLL interaction. In conjunction, we have exploited the co-crystal structure of the menin-MLL peptide complex (20) to design and improve iMen for its selectivity and potency.

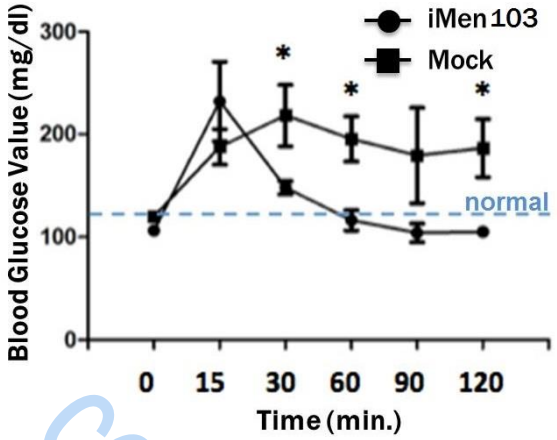


Fig 3: iMen103 significantly improves the function of the islets of NOD mice *in vivo* as shown in glucose tolerance test (GTT). NOD mice were injected Intraperitoneally (I.P.) with 60mg/kg body weight iMen103 (●iMen103) or vehicle control (■MOCK) (9 week-old NOD injected daily for 9 weeks). Two groups of NOD mice (n=4/group) were set up. Mice were treated daily with either vehicle (20% DMSO, 25% PEG400, 55% PBS in 100 µl, ■Mock), or with iMen103 (60 mg/kg bw in vehicle, ● iMen103). The results indicate that treatment with iMen103 significantly ameliorated the random blood glucose level at weeks 9 and 10, when the control group started to develop high blood glucose level, preventing the onset of the hyperglycemia prior to the end point of the experiment. iMen103 improved the function of the pancreatic islet in NOD mice, as compared to the mock group, the treated group showed normalized glucose tolerance test (GTT).

<u>iMen normalizes the blood glucose level in non-obese diabetic mice (NOD) and Diet Induced Obese (DIO) mice:</u> iMen (iMen103) improved the function of the pancreatic islet in NOD mice, as compared to the mock group, the treated group showed normalized glucose tolerance test (GTT) (Figure 3). In order to determine whether the treatment with iMen102 affects glucose stimulated insulin secretion (GSIS), the mock and iMen103 treated mice were injected with glucose (I.P.), and then monitored for blood insulin level. Figure 4 shows that we injected BrdU (50 mg/kg body weight) into the NOD mice 18 hour before the end point of the studies, and the mice were sacrificed and the pancreata were collected to stain for insulin-expressing and BrdU positive cells, as previously described (1).

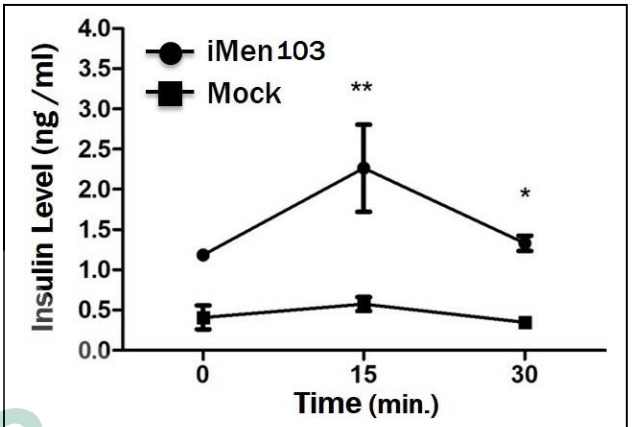


Fig 4: iMen103 markedly increased insulin level detected in blood upon glucose stimulation in NOD diabetic mice *in vivo*. NOD mice were injected Intraperitoneally (I.P.) with 60mg/kg iMen103 (● iMen103) or vehicle control (■MOCK) (9 week-old NOD mice injected daily for 10 weeks. To determine whether the treatment with iMen102 affects glucose stimulated insulin secretion (GSIS), the mock and iMen103 treated mice were injected with glucose (I.P.), and then monitored for blood insulin level. Result shows that iMen103 markedly increased insulin level in blood diabetic mice *in vivo*.

The results indicate that the iMen103 treated mice showed significant increase of BrdU positive cells as shown in Figure 5A and 5B. These results strongly suggest that treatment with iMen102 can prevent the onset of hyperglycemia in NOD mice by increasing beta cell regeneration and insulin secretion. To determine whether the impact of iMen102 on ameliorating diabetes in T2D model, we chose to investigate the impact on diet (high fat)-induced obese (DIO) mice, a commonly used T2D diabetes model. To this end, we treated the DIO mice (from Jackson Lab) with either

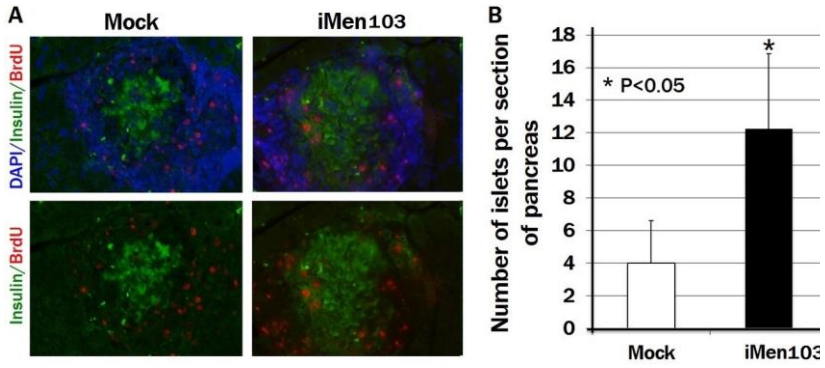


Fig 5: iMen103 increased beta cell regeneration and resulted in higher insulin production. (A) *Immunofluorescence staining of Non Obese Diabetic (NOD) mouse pancreas* in 10 weeks old female mice were treated via IP with iMen103 (60kg/kg bodyweight) or Mock (not treated) daily, followed by collection of pancreata, and immunostained with anti-insulin and BrdU antibodies. (B) *Analysis of islet number in mock or iMen103 treated NOD diabetic mice* showing a statistical significant ~3 fold increase with P<0.05 in the number of islet cells per section of pancreas measured in iMen103 treated versus mock. to determine whether iMen103 treatment affects the beta cell regeneration, BrdU (50 mg/kg body weight) was injected into the NOD mice 18 hour before the end point of the studies, and the mice were sacrificed and the pancreata were collected to stain for insulin-expressing and BrdU positive cells, as previously described (1). The results indicate that the iMen103 treated mice showed significant increase of BrdU positive cells. Treatment with iMen103 can prevent the onset of hyperglycemia in NOD mice by increasing beta cell regeneration and insulin secretion.

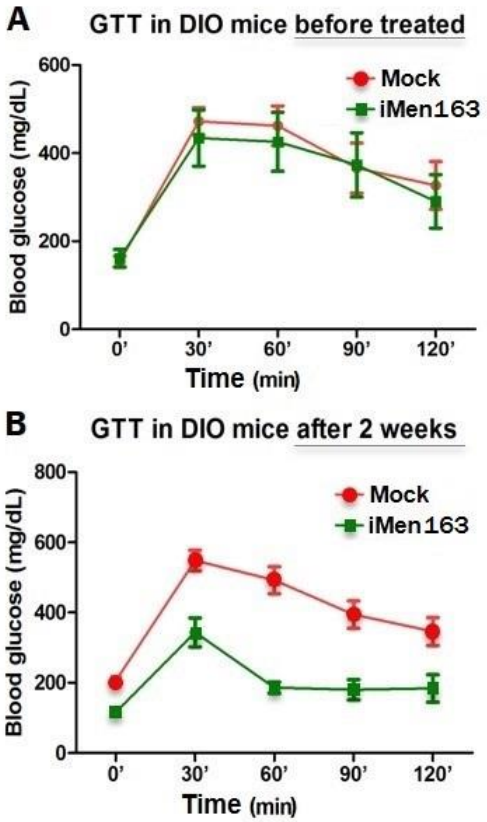


Fig 6: iMen163 markedly increased insulin level detected in blood upon glucose tolerance test (GTT) in the DIO diabetic mice *in vivo*. (A) GTT for (Mock) group or the experimental (iMen163) group of the DIO mice before treatment. **(B)** GTT after daily intraperitoneal injection (I.P.) with 70 mg/kg iMen163 () or Mock () at the age of 3 week-old on daily basis for 2 weeks. Treatment with iMen103 can prevent the onset of hyperglycemia in NOD mice by increasing beta cell regeneration and insulin secretion. To determine whether the impact of iMen103 on ameliorating diabetes in T2D model, we chose to investigate the impact on diet (high fat)-induced obese (DIO) mice, a commonly used T2D diabetes model. To this end, we treated the DIO mice (from Jackson Lab) with either vehicle or iMen163 (n=7 for Mock, and 8 for iMen103 group). The mice (12 wks) for each group were evaluated for GTT before treatment for each group, and both group showed impaired GTT in (A). We treated the mice with either control vehicle (Mock) or with iMen163 (in vehicle) daily for 10 days, and then both groups were tested for GTT. In (B) after iMen163 was I.P. administered daily to the DIO mice for 10 days, while the mock group still had the impaired GTT, notably, the treated group had normalized GTT, indicating that the iMen163 treatment markedly ameliorated the diabetic conditions in the DIO mice.

vehicle or iMen163, as described in Figure 6 (n=7 for Mock, and n=8 for iMen103 group). The mice (12 wks) for each group were evaluated for GTT before treatment for each group, and both group showed impaired GTT (Figure 6A). We treated the mice with either control vehicle (Mock) or with iMen163 (in vehicle) daily for 10 days, and then both groups were tested for GTT. Figure 6B shows that after iMen163 was I.P. administered daily to the DIO mice for 10 days, while the mock group still had the impaired GTT, notably, the treated group had normalized GTT, indicating that the iMen102 treatment markedly ameliorated the diabetic conditions in the DIO mice. Further experiments are ongoing to determine the impact of cell regeneration *in vivo*, laying down strong foundation to develop potent iMen to treat diabetes. Nevertheless, these latest results are the first to prove the principle that iMen can increase

beta cell regeneration and GSIS. Going forward we intend to identifying and optimizing our iMen compounds to derive the most favorable drug like properties.

iMen increases human beta cells regeneration: Ultimately, we want to determine if iMen can also work in regenerating human beta cells and manage blood glucose level as seen in our NOD mouse experiments *in vivo* as shown in Figure 3, 4, and 5, and in the DIO mouse as shown in Figure 6. In Figure 7, we showed that human islets from a donor were cultured *ex-vivo* and treated with 0nM iMen102, with 250nM iMen102, and 500nM iMen102 for 7 days, all in the presence of vehicle DMSO (0.5%). qRT-PCR analysis of the control and treated islets showed the increase level of Ki_{67}, a marker for proliferating cells, suggesting that increasing concentration of iMen102 treatments also leads to an increased replication of human beta cells. In sum, menin – MLL inhibitors as drug leads have been identified via structure-based rational drug design. Studies also have been done by co-founder Professor Hua at the University of Pennsylvania demonstrating that iMen class of compounds could reverse diabetes in two different animal models: Non-Obese diabetic mouse model (NOD) T1D and Diet Induced Obese (DIO) T2D experiments. Additionally, in a human ex-*in vivo* menin-MLL inhibitor has shown promise to regenerate human beta cells as shown in Figure 7.

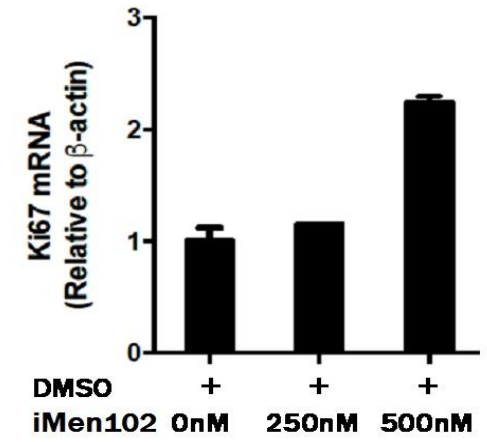
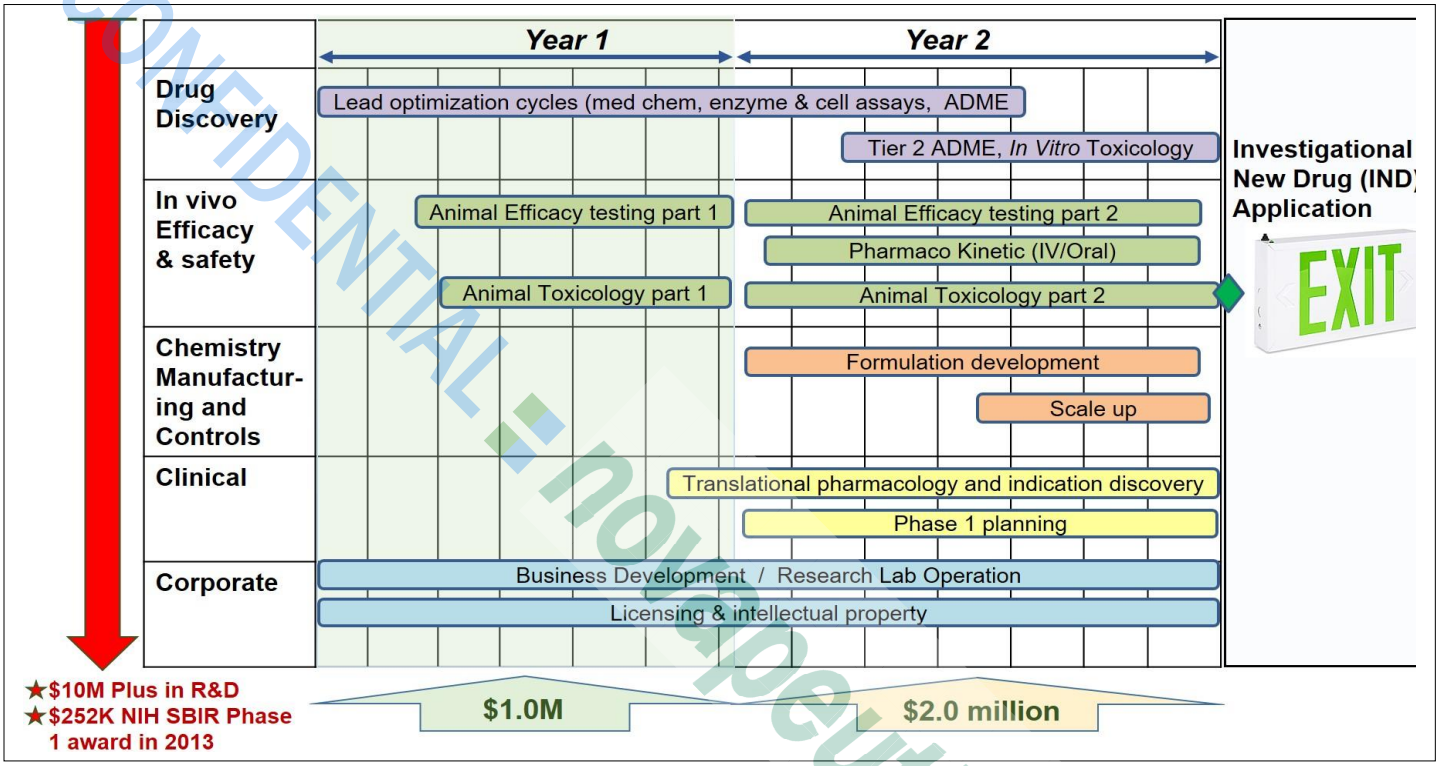


Fig 7: iMen102 induces regeneration of human islet cells. Treatment of human islets isolated from an 11 year old donor for 7 days in culture medium, with either DMSO alone or plus iMen102 at 250nM or 500nM, followed by isolation of RNA and RT-PCR to detect the level of Ki67, a well-known marker for cell proliferation. Human islets from a donor were cultured *ex-vivo* and treated with 0nM iMen102, with 250nM iMen102, and 500nM iMen102 for 7 days, all in the presence of vehicle DMSO (0.5%). qRT-PCR analysis of the control and treated islets showed the increase level of Ki67, a marker for proliferating cells, suggesting that increasing concentration of iMen102 treatments also leads to an increased replication of human beta cells.

DEVELOPMENTAL PLAN

The initial data package obtained from further funding would provide clarity needed to enter into a full Investigational New Drug (IND)-enabling studies, with the goal to eventually filing the IND application with the FDA to initiate the clinical studies. At the start, as shown in the flow chart below, our small molecule therapeutic candidates are to be subjected to lead optimization cycle. This refinement is critical for maximizing the final drug candidate(s) prospect for success through clinical trials. In Year 1 the small molecule candidates' therapeutic properties will be validated and refined through parallel developments using medicinal chemistry, enzyme and cellular assays and ADME tests (absorption, distribution, metabolism, and excretion);



followed by pharmacokinetics and toxicological studies both *in vitro* and in the T2D animal models.

Novapeutics aim to complete iMen optimization and finish pre-clinical development by the end of 2020, as seen in the flow chart above. We estimate that it will take around $3.0 M in the next two years to complete the IND enabling studies with GLP animal studies in Year 2. Once optimized iMen(s) is identified, there will be a need to formulate the compound to make it closer to having the desirable chemistry and scale up its production for clinical trials. Some early and smaller groups of animal efficacy and toxicology tests will be completed in parallel. The expected completion time of Clinical Phase I, II, and III is one, two and four years, respectively.

COMPETITION AND ADVANTAGE

a. Conventional diabetes drugs

Conventional T2D treatments listed below utilize various mechanisms of action that all aim to maintain normal blood glucose levels. However, no treatment addresses the major underlying cause of disease, which is continuing destruction of the insulin-producing pancreatic beta cells. Although there are other injectables beside insulin, it remains the most popular and effective treatment to date for mid to late stages. Meanwhile, other treatments that are administered orally and primarily used for early and intermediate stage T2D.

Insulin	Advanced T2D is currently treated with insulin in its various forms. Insulin, has a variety of side effects, including severe hypoglycemia(21), retinopathy, and weight gain. Since T2D is a progressive illness, patients must take insulin for the rest of their lives. Studies have indicated that patients associate insulin treatment with loss of personal freedom, worsening of the disease and onset of complications. 85% of T2D patients have characterized their initiation of insulin treatment as a personal crisis (22).
Metformin	Metformin belongs to the class of anti-diabetes drugs called biguanides. It has very few side effects except gastrointestinal upset. It is most effective in early stage T2D. It is believed to be the most widely prescribed anti-diabetes drug in the world. Metformin acts by decreasing glucose production in the liver. This leads to increased insulin sensitivity and, in turn, enhanced peripheral glucose uptake. Metformin is considered an indirect intervention because it does not stimulate endogenous insulin secretion. Metformin is prescribed along with a number of other oral drugs to treat more advanced stage patients.
Sulfonylureas	This is a class of drugs that increases insulin release from pancreatic beta cells by binding to an ATP-dependent channel on the cell membrane that increases insulin secretion. Side effects include: increased risk of hypoglycemia as a result of excess insulin production and release, weight gain, abdominal upset, headache and hypersensitivity reactions, and according to some experts accelerated beta cell loss (23).
GLP1 / GIP agonists	Glucagon-like Peptide-1 (GLP1) and Gastric Inhibitory Peptide (GIP) agonists belong to a class of molecules called incretins that activate the secretion of insulin. GLP1 agonists bind to the pancreatic cell membrane GLP receptor activating secretion of insulin. Exenatide (marketed as Byetta) and Liraglutide (marketed as Victoza) are GLP1 agonists that are injected subcutaneously into the body. Side effects include a decrease in gastric motility, nausea, and undesirable weight loss for some.
Dipeptidyl Peptidase-4 (DPP4) inhibitors	DPP4 is an enzyme that inactivates the action of GLP1 and GIP, which activate insulin secretion. DPP4 inhibitors developed include: Vildagliptin (marketed as Galvus), Sitagliptin (marketed as Januvia), and Saxagliptin (marketed as Onglyza), which increase the blood concentration of GLP1. DPP4 inhibitors have milder side effects compared with GLP1 agonists, but when used in combination with sulfonylureas have been known to lead to weight gain and/ or hypoglycemia.
Sodium/ Glucose Co-transporter 2 (SGLT2) inhibitors	SGLT-2 inhibitors act as indirect antidiabetes drugs by blocking glucose re-uptake from renal tubules, and hence excess glucose is lost in the urine. This reduces the need for secreting more insulin, but can have some side effects such as mild weight loss, a mild reduction in blood sugar levels with a slight risk of hypoglycemia. Urinary tract infection is another common side effect. Examples of SGLT-2 inhibitors are Canagliflozin (marketed as Invokana) and Dapagliflozin (marketed in Europe as Forxiga).

b. New-to-Market and Developmental stage diabetes treatments

Although there are 128 medicines in development for diabetes (24), we list highlighted technologies below in a table that potentially can be in competition with iMen:

Competitions Medicine	Sponsor	Indication	Development Phase
Afrezza (insulin inhalation)	MannKind Valencia, CA	T1D, T2D	Market*
HIP-2B (human pro-islet peptide) (injectable)	CureDm Wilmington, DE	T1D, T2D	Phase Ib
NN1953, NN1954 (oral insulin)	Novo Nordisk, Plainsboro, NJ	T1D, T2D	Phase II
Oral-Lyn^{R} (oral insulin)	Generex Biotechnology Toronto, Canada	T1D	Phase III
ORMD 0801 (oral insulin capsule)	Oramed Jerusalem, Israel	T2D	Phase III
NN9924 (oral variant of Liraglutide)	Novo Nordisk Plainsboro, NJ	T2D	Phase II
Solo Micro-pump (micro-pump insulin delivery system)	Medingo Ltd. Yoqneam, Israel	T1D, T2D	FDA approved
U-strip Insulin Patch (noninvasive insulin delivery system)	Transdermal Specialties, Norwalk, CT	T1D, T2D	Phase II
*In the 9 months of sales after FDA approval, inhalable insulin Afreeza sold around $5M in revenue. Under performing the joint distribution agreement between MannKind and Sanofi, and was terminated in 2016.			

c. Oral drug landscape

Existing oral drugs for T2D are used in the early stages of the disease while advanced T2D patients largely rely on the injectables insulin. The Novapeutics technology provides an oral alternative for advanced T2D patients. Consequently, Novapeutics' main direct competitors are the major players in the injectable insulin market in United States, namely Novo Nordisk (37% US by value, 44% worldwide), Eli Lilly (26% US by value, 22% worldwide) and Sanofi (37% US by value, 33% worldwide) (25). Major diabetes products sold by these companies worldwide are listed below. Oral treatments for early diagnosed diabetics, such as Metformin, are also listed below.

Drug name	Generic	Company	Therapeutic class	Administration	Frequency
Januvia+ Amaryl-m	Sitaglipin + metformin+ glimepride	Merck & Co	DPP4 Inhibitor	Oral	Daily
Onglyza	Saxagliptin	Bristol-Myers Squibb and AstraZeneca	DPP4 Inhibitor	Oral	Daily
Nesina	Alogliptin	Takeda	DPP4 Inhibitor	Oral	Daily
Tradjenta	Linagliptin	Boehringer Ingelheim	DPP4 Inhibitor	Oral	Daily

Galvus	Vildagliptin	Novartis	DPP4 Inhibitor	Oral	Twice Daily
Byetta	Exenatide	Bristol-Myers Squibb	GLP-1 Agonist	Injection	Twice Daily
Bydureon	Exenatide	Bristol-Myers Squibb	GLP-1 Agonist	Oral/Injection	Twice Daily
Victoza	Liraglutide	Novo Nordisk	GLP-1 Agonist	Oral	Daily
Lyxumia	Lixisenatide	Sanofi	GLP-1 Agonist	Injection	Daily
Lantus	Insulin Glargine	Sanofi	Insulin	Injection	Daily
Levemir	Insulin detemir	Novo Nordisk	Insulin	Injection	Twice Daily
Tresiba and Ryzodeg	Insulin degludec	Novo Nordisk	Insulin	Injection	Daily

d. Potential immediate competitions

There are a number of companies with approved therapies for advanced T2D with an oral method of administration (e.g., oral insulin, inhalable insulin, and an oral variant of liraglutide). A remarkable example is Afrezza by Mannkind, recently approved by the FDA. In early 2016, Afrezza did not meet the U.S. distribution and marketing partner Sanofi's expectation and deal was terminated. Current available oral diabetes treatments are at the early-stage of T2D, which constitutes 58% of the market share (5). Early-stage T2D oral drugs are not our direct competitors, where this could be a potential market for iMen.

Besides replacing injectable insulin or liraglutide with oral variants, there is another therapy in development in the area of pancreatic beta cell regeneration that would compete directly with Novapeutics. This therapy consists of injecting human peptide HIP-2B, which can stimulate the regeneration of pancreatic islets. It is being developed by CureDM, and is currently just came out of the Phase IB clinical trial in 2016. The CureDM technology was licensed by Sanofi-Aventis for $335 million 2010. Further details on this deal can be found at the end of this document in the section of benchmarking examples.

In T1D, the immune system adversely reacts to destroy pancreatic beta cells. Research in this area has focused on developing immunosuppressant drugs, as well as employing transplantation of stem cells and gene therapy techniques to kick-start insulin production. Such regeneration techniques are expected to compete directly with Novapeutics technology. For example, Living Cell Technologies based in New Zealand had received approval to conduct phase II clinical trial in 2014 for a technology called Diabecell, which consists of encapsulated porcine islets (insulin producing cells) implanted into a patient's abdomen using a simple laparoscopic procedure. A study conducted in Brazil at the University of Sao Paulo has shown that transplanted stem cells can kick-start insulin production by the pancreas. Although the number of subjects

for this study was small, the results are promising(26). As cited in a recent report, there are 19 products in development for cell and stem cell therapies (27): Four are islet cells, ten are various adult stem cells and their progeny, and five are embryonic-like stem cell-derived insulin-producing cells. Out of 10 products using adult stem cells, only three are auto-transplants, significantly less than in other adult stem cell–based pipelines (27).

Medtronic and Roche have been developing an artificial pancreas system that consists of: 1) real time monitoring of insulin, 2) a computer system that can decide how much insulin to inject, and 3) an insulin pump that can accurately respond to such instructions. There are various technological hurdles towards achieving such a system though, for example, an accurate sensor that works internally in the patient's body, software directions accurate enough to avoid overdosing, as well as a counter-regulatory mechanism to counteract an overdose (26).

iMen chemical composition wise, there are currently two menin-MLL inhibitor patents that are under active development for a better leukemia treatment and both are in the preclinical stage: (1) One was published on December 18, 2014 with priority date of June 12th, 2013 by The Reagents of the University of Michigan and Vanderbilt University (28), under development by the Kura Oncology for the leukemia treatment; and (2) One was published on June 29, 2017 with priority date on December 22nd, 2015 by the Vitae Pharmaceuticals, Inc. (now Allergan), under development by the Syndax Pharmaceuticals (29).

e. Intellectual property protection

Novapeutics is developing strategies that will enable the creation of a comprehensive strong intellectual property portfolio. Through this funding, we will be able to advance our provisional patent applications on our iMen compounds. We anticipate filing formulations patents and other applications as we continually assess and identify patent subject matter during our drug development program.

f. Future financing and strategic partnering

Novapeutics plans to complete IND enabling studies and is projected to be ready for its final drug candidate by the end of 2020. Initial funding will be needed at the beginning of the 2nd quarter of 2018 to prosecute our patent and conduct pre IND-enabling studies, such as *in vitro*, ADME, and non-GLP animal studies. Later, in order to fully cover the costs of clinical trial costs. According to extensive research on current oral drugs treating T2D, the estimated time of completion and approximate costs of clinical trials Phase I (20-80 volunteer patients), Phase II (100-300 volunteer patients) and Phase III (1000-3000 volunteer patients) is one year - $2M, two years - $14M, and four years - $186M, respectively. This data is

based on estimated clinical trial expenditures for GLP-1 analogues in diabetes incurred by big pharma companies (Amylin, Novo Nordisk, Ipsen, and Roche)(30). Novapeutics plans to actively seek strategic partnering through product licensing or joint ventures, in order to partially or fully cover these costs by one of the allied parties. Below are two benchmarking examples:

Benchmarking Example 1: Exelixis's deal with Bristol-Myers Squibb Company Exelixis secured a product licensing deal with Bristol-Myers Squibb (BMS) for the development and commercialization of a T2D oral drug in 2010 while the drug was still in the preclinical process. BMS was responsible for further research, development, commercial and manufacturing activities. The financial structure of the deal allowed Exelixis to receive development and regulatory milestone payments of up to $250 million and commercial milestones of up to $150 million while receiving an upfront cash payment of $35 million from BMS.

Benchmarking Example 2: CureDM deal with Sanofi-Aventis CureDM is a biopharmaceutical company devoted to developing therapies to replace insulin secured a licensing deal worth $335 million with the French biopharma company Sanofi-Aventis in June 2010. According to the terms of this deal, Sanofi secured the rights to develop and market Pancreate — a first-in-class peptide therapeutic that may have the potential to stimulate pancreatic islet neogenesis — for the treatment of T1D and T2D in humans and animals. At the time of the deal, the development of Pancreate was at preclinical stage and the terms of deal included an undisclosed upfront payment, success-based development, regulatory and sales performance milestones for a total of up to $335 million. At the signing of the contract, the agent was at the end of the preclinical stage and entered phase I at the end of that year.

g. Significant advantages

iMen could increase the number of functional beta cells in the advanced T2D patients, eliminating the need for repeated injections of exogenous insulin analogues. The use of iMen to interrupt menin and MLL interaction will enhance the pancreatic islet mass and function by regenerating beta cells. In summary, our intended final product would be orally active and this means that the advance patients can avoid invasive medical procedures (i.e. surgery) to reverse diabetes, such as implanting an insulin pump or beta cells transplantation.

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