Addendum

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Drug Development

10-Year Development of Life-Saving Drugs

A 10-Year Demonstration Project to rapidly develop and make available to patients safe, effective, and affordable advanced drugs for many severe and life-threatening diseases

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Summary

Developing, testing, and obtaining regulatory approval for a conventional breakthrough drug typically takes 10 to 20 years and costs over $1 billion. Because of these long times and high costs, drugs for many rare diseases can never be developed by a conventional drug development route because they cannot provide an adequate return on the huge required investment.

Technological advances over the last few decades are expected this year to make possible a new drug development strategy wherein precision-targeted drugs for severe and life-threatening diseases can be rapidly and cheaply developed and made available to patients - giving patients a **right-to-live** opportunity virtually unavailable via a conventional drug development route.

This new drug development strategy includes four key elements:

1) Design and produce precision-targeted drugs which specifically bind selected RNA transcripts. Such drugs can be designed and produced in a few days to weeks for a few thousand dollars. Because the mechanism by which they bind to their biological targets is precise and predictable, such drugs provide exquisite specificities typically hundreds of fold greater than the specificities afforded by the conventional small-molecule drugs which comprise most current pharmaceuticals.

2) Confirm in an appropriate biological test system that each such drug effectively and specifically blocks its biological target.
3) Develop, with very little added time and cost, an antidote to quickly, specifically, thoroughly, and inexpensively halt the action of each drug - where such antidote is to be readily available in the unlikely event the administered drug is found to cause a serious adverse effect in the patient.
4) Implement a novel & practical method to rapidly get these precision-targeted drugs to patients at far lower costs than is currently possible - while providing greater benefits and lower risks than afforded by many current FDA-approved drugs.

The time and cost problem in drug development

A breakthrough drug is one which treats a presently un-treatable disease, or provides a great improvement over present treatments for a serious disease. Currently development of a breakthrough drug requires about 10 to 20 years and costs up to a billion dollars - in large part because of clinical testing and regulatory approval costs. Consequently, most newly discovered drugs, no matter

how beneficial they might be to patients, will never be developed because they cannot provide an adequate return on the huge investment that would be required for their testing and regulatory approval. Only the few drugs which satisfy specific and demanding **business** criteria can be developed. Those criteria are: i) a large patient population; ii) a strong patent position; and, iii) a largely untapped market. Regrettably, because of the huge time and costs of developing a new drug, a drug's benefit to patients can only be a minor consideration in deciding whether or not to develop that drug.

New precision-targeted drugs for many diseases

Beginning in 1944 great advances have been made in our understanding of how organisms function at the molecular level. Building on that broad understanding of life at the molecular level, in 1978 a key advance in drug design was described which makes it possible to rapidly and inexpensively devise, produce, and test precision-targeted drugs for a host of severe and life-threatening diseases. A drug of this new type, comprising 15 to 30 linked genetic letters, is called an **"antisense drug"** because it can precisely target the **"sense"** sequence of genetic letters of a selected RNA transcript.

This high-precision targeting of a selected RNA genetic sequence exploits what is commonly referred to as Watson-Crick pairing between the four genetic letters (A pairs with T, and C pairs with G) which underlies the function of all genetic material - from viruses to humans. This antisense drug design strategy is illustrated in the figure below.

In principle, one can target any selected RNA genetic sequence simply by assembling 15 to 30 genetic letters in a sequence complementary to 15 to 30 genetic letters of the RNA genetic sequence to be targeted. **In practice**, to make useful drugs required decades of effort to re-design the structure of natural genetic material to achieve the key properties needed for therapeutic use - and the antisense structural type with the best of these key properties (Morpholinos) required a quite radical re-design of natural genetic structures.

A precision-targeted antisense oligo can be used to easily and precisely
target a single gene transcript within a cell - generally without affecting any of the more than hundred thousand other gene transcripts in that cell. Precisely targeting a single gene transcript can prevent the synthesis of a particular protein - which can serve to kill an infecting virus or halt an invading cancer. Alternatively, targeting a different type of site (a splice site) in a selected RNA transcript can suppress a mutant protein and instead generate a functional protein. Such targeting can be used for treating genetic defects such as underlie muscular dystrophy, spinal muscular atrophy, thallasemia, Huntington's disease, progeria, and others.

Such precision-targeted antisense drugs can provide patients with safe, effective, and affordable drugs for a host of severe and life-threatening diseases. This technology also allows rapid (a few days) and relatively inexpensive design and production of a custom drug for an individual patient suffering from a new strain of a virus, or suffering from a mutation specific to that patient. Such drugs promise an era of personalized medicine.

Thus, it is particularly vexing that in our current drug regulatory system
most of the possible drugs of this new antisense type can never be made available to patients because of the exorbitant costs needed for FDA-mandated multi-phase clinical testing, plus the excessive time required for obtaining regulatory approvals at each phase of the process. Those exorbitant time and cost requirements effectively assure that many patients with currently un-treatable life-threatening diseases will never benefit from easily designed, developed, and produced advanced antisense drugs which could likely provide many patients with a safe, effective, and affordable cure (a **right-to-live**).

Precision drugs can avoid time and cost problem

Because of fundamental advantages inherent in this novel antisense drug design strategy, I contend that for an antisense drug it is possible to rigorously, quickly, and affordably assess efficacy and dramatically reduce risk to the patient - to a level that matches or exceeds current FDA standards. I also believe this can be achieved in days to weeks (instead of the years required for conventional drugs) and for just thousands of dollars (instead of the hundreds of millions to billions of dollars required for conventional drugs).

Time and cost barriers currently preclude the development of many advanced life-saving drugs for rare diseases - drugs which are now possible due to recent

advances in the life sciences.

GENE TOOLS, LLC intends to remedy this lack of life-saving drugs for rare and life-threatening diseases by carrying out a novel 10-year **Right-To-Live** demonstration project wherein we (and collaborating research groups) will:

a) devise, develop, produce, and test a substantial number of advanced precision-targeted antisense drugs for severe and life-threatening diseases;

b) demonstrate that the efficacy of these drugs can be rapidly, rigorously, and quantitatively assessed at the molecular level at modest cost;

c)demonstrate a method for dramatically decreasing risk to patients by providing a means to quickly, thoroughly, and specifically de-activate any such drug within the patient - to be used only in the unlikely event that particular drug causes an adverse reaction in the treated patient; and,

d) combine the above into a complete system for developing advanced antisense drugs and delivering them at affordable prices and in a timely manner to patients suffering from severe and life-threatening diseases.

This demonstration project is expected to:

a) provide many patients with advanced antisense drugs for safe, effective, and affordable treatment of a host of severe and life-threatening diseases - thereby quite soon

providing those patients a true **Right-To-Live** opportunity that would otherwise be precluded by regulatory, patent, financial, and/or other obstacles and delays that stymie conventional drug development;

b) greatly reduce the cost of new high-specificity drugs for a wide range of serious diseases which currently cannot be safely or effectively treated;

c) provide on-demand rapid-response drugs for virtually any viral disease (or new strain) - such as might be rampant during a major epidemic, or might be used as bio-warfare agents by terrorists or rogue nations; and,

d) help to substantially reduce the price of advanced drugs for serious and life-threatening diseases, and help avoid bankruptcy of our country's healthcare system - and other healthcare systems around the world.

"Right-To-Live" Demonstration Project to develop antisense drugs for severe & life-threatening diseases

Following is our "**Right-To-Live" project** for making available to patients affordable and personalized drugs for severe and life-threatening diseases.

A. Therapeutics for severe & life-threatening diseases

GENE TOOLS, LLC will devise and develop prospective therapeutics for severe and life-threatening diseases. Generally a therapeutic for a given disease will be

developed in collaboration with one or more research groups focused on that disease. As has been the case for our multiple collaborations over the past 15 years, the collaborating research group(s) will provide detailed knowledge of the molecular mechanism underlying the selected disease. GENE TOOLS will then design and produce a set of advanced delivery-enabled antisense oligos optimized to block or otherwise treat that disease. Then the collaborating research group(s) will carry out testing of these antisense oligos in their already-developed biological test systems specific for that disease.

With the advent of new advances in our in vivo delivery technology now nearing completion, I estimate that in 2016 a dozen or more such prospective delivery-enabled antisense therapeutics will be developed to the stage of demonstrated safety and efficacy in animals - at a cost of only a few
tens of thousands of dollars for each such drug. This short time and low cost compares very favorably with the multiple millions of dollars and multiple years it takes conventional drug companies to develop a single small-molecule lead drug and demonstrate its safety and efficacy in animals.

At first glance it might appear to be just a wild pipe dream that one small biotech company, in cooperation with suitable collaborating research groups, will be able to develop a dozen or more new breakthrough drugs through the initial animal testing stage in one year at a total cost of less than a million dollars. Nonetheless, to put this in perspective it should be appreciated that over the past 15 years GENE TOOLS, LLC has designed,

produced, and shipped over a hundred thousand custom-sequence gene-modulating antisense oligos targeted against tens of thousands of different genes in dozens of different species ranging from viruses to humans. These antisense oligos have been used by thousands of our customers (research scientists) in hundreds of laboratories around the world - leading to publication of over 7,500 research papers (see:http://pubs.gene-tools.com).

A substantial number of those 7,500 research papers focused on use of these precisely targeted and exquisitely specific antisense oligos to selectively shut down a number of very nasty viruses - such as ebola, marburg, dengue, and many others which are of national defense concern because of their potential for use by terrorists. Our antisense oligos are also widely used to correct severe genetic defects - such as underlie thalassemia, muscular dystrophy, spinal muscular atrophy, Huntington's disease, and progeria. These antisense oligos are also used to selectively block numerous genes which play a key role in a variety of cancers. Our antisense oligos are also being used to block or alter the synthesis of tau protein in brain cells to halt progressive killing of neurons in Alzheimer's disease and related dementia conditions. Notably, one of our antisense oligos has been used to block synthesis of that tau isoform which forms the cytotoxic tau tangles within neurons. That antisense oligo achieves this by targeting a splice site which induces a shift to synthesis of the fully functional tau isoform which does not form tau tangles.

It should be obvious that many of these published studies

hold promise for therapeutic applications - but to date the published research results are of interest primarily just to scientists studying the molecular mechanisms underlying such diseases and conditions. This is because antisense oligos currently are of little or no practical therapeutic value for actual human patients because of limitations in current delivery technologies - which cause significant toxicity and achieve only poor efficiency. As a consequence, the generally-very-safe antisense oligos cannot yet be safely and/or efficiently delivered into the proper subcellular compartment of cells in patients.

However, when we launch our new in vivo delivery system, expected to be completed in 2016 (see Appendix 2), I believe our antisense oligos will go from being just very useful research tools - to also providing an unprecedented flood of breakthrough drugs for the diseases noted above, as well as for many other diseases already studied and widely published on by research scientists around the world.

B. Conventional preclinical testing

If and when our or other's experimental results indicate good safety and efficacy for a given prospective drug in cultured cells and in small animals, we or our collaborating research group will next carry out, or contract out, conventional preclinical testing in non-humans (toxicity, pharmacokinetics, and pharmacodynamics). This conventional preclinical testing will also be buttressed by more rigorous and quantitative molecular biology assays of efficacy and

specificity.

C. Carry out key operations in an independent nation

If preclinical test results for a new drug show that its benefits substantially outweigh its risks, then we intend to set up operations for producing, testing, and using that drug in humans. For this demonstration project to be affordable I believe it is essential to carry out the remaining clinical steps for each drug within an independent nation (ie., outside the jurisdiction of US Government agencies). This avoids the many obstacles and delays which currently make drug development so very slow and exorbitantly expensive, and which prevents development of custom drugs for personalized medicine.

Probably only after this demonstration project is successful, and safety and efficacy in patients is persuasively demonstrated in an independent nation, will it be possible to persuade US regulators to embrace these new testing and
risk-reduction methods for developing these precision-targeted antisense drugs.

The facilities and key operations in the independent nation will include:

i) a production facility to produce high-quality sterile drug products, each with rigorously confirmed sequence, structure, purity, and sterility;

ii) a facility for carrying out streamlined and affordable clinical testing; and,

iii) a facility for treating patients. After objective evidence indicates a given drug has good efficacy, and an antidote is on hand to quickly halt any adverse effects which might arise, that drug will be used to treat patients who have traveled to our treatment facility in the independent nation.

D. Crucial "first-in-human" efficacy testing

A drug to be used for treating a severe or life-threatening disease or condition should have rigorous, objective evidence demonstrating that the benefits of that drug substantially outweigh its risks. For a conventional drug having an expected market of a billion or more dollars per year, the company developing that drug generally had to spend one to two decades and many hundreds of millions to more than a billion dollars carrying out FDA-mandated multi-phase clinical trials designed to thoroughly assess safety (risks) and efficacy (benefits) for just that single drug.

However, a great many drugs which could offer potentially great benefits to a wide variety of patients can never be developed by the conventional route because such drugs individually serve only a small patient population and/or have a limited (or no) patent coverage. If such drugs are to be developed and made available to patients at affordable prices, then rigorous evidence for

each drug's benefits, and some means to assure acceptably low risks, must be obtainable at a vastly lower cost in time and money than is currently possible with the present exorbitantly expensive FDA-mandated multi-stage clinical trials, costs which are further increased by the required time-consuming regulatory approvals at each stage.

GENE TOOLS' Morpholino-type antisense oligos act by very specifically binding to and blocking the function of a targeted sequence of the RNA transcript of a selected gene. This binding to the target sequence is by the pairing mechanism first described by Watson and Crick in 1953. Because of this precise and predictable mechanism of action, antisense drugs can provide exquisite specificity for their targeted genetic sequences - with specificities that can be hundreds of fold greater than provided by the
typical small-molecule drugs that comprise most current pharmaceuticals.

For a drug to be used for treating a severe or life-threatening disease it is essential that there be rigorous, objective evidence that the drug has good efficacy. In sharp contrast to conventional drugs, in the case of antisense drugs a number of widely-used molecular biology assays can quickly and quantitatively confirm each drug's therapeutic efficacy at the molecular level. A number of molecular biology techniques can provide rapid and inexpensive confirmation that a given antisense drug is very selectively binding its targeted genetic sequence in cultured cells and in animals. These include: western blots utilizing fluorescent antibodies;

northern blots using radioisotope-labeled probes; reverse transcriptase/polymerase chain reaction for assessing alteration of splicing; and, simple virus titer assays. Such methods, widely used in molecular biology labs, provide reliable quantitative assessments of how well a given antisense drug is binding its targeted RNA transcript - thereby confirming at the molecular level that the antisense drug is achieving its intended action in the treated subject.

Additional conventional assessments of therapeutic efficacy will also be used. However, compared to the above-described molecular-level assays, the conventional assessments typically used in clinical trials provide less decisive, less quantitative, and more subjective evidence for the efficacy of a drug.

E. Risk-reduction method to quickly, thoroughly, and specifically de-activate the antisense drug

Risks from potential adverse effects due to any given antisense drug can be dramatically reduced by providing a means to quickly, thoroughly, precisely, and affordably halt the activity of that drug within the patient. Such a means comprises the sense oligo complementary to the antisense drug. When that sense oligo is administered to a patient who is exhibiting an adverse effect from an antisense drug, that sense oligo, on encountering the antisense drug within the patient's cells, quickly pairs with the antisense drug to form an inert duplex. This process effectively de-activates the antisense drug and thereby

halts the undesired adverse event - as illustrated below.

Risk-reduction method

Such a sense oligo would only be used in the unlikely event an antisense drug caused a significant adverse effect in a patient. However, simply having such a sense oligo available provides a tremendous risk-reduction benefit to the patient by allowing a rapid and specific de-activation of the antisense drug within the patient on the rare occasion when it might be needed.

A means for equivalent risk-reduction with conventional small-molecule drugs (comprising most current drugs) is generally very difficult and expensive to develop, and effective "antidotes" for small-molecule drugs have only been achieved in a few instances. This is in spite of the FDA having recently begun to encourage pharmaceutical companies to attempt to co-develop companion antidotes in their new drug development programs.

In sharp contrast, in the antisense drug development strategy designing the risk-reducing sense oligo takes only a few seconds. That risk-reducing sense oligo is then synthesized at the same time as its complementary antisense drug. Finally, in the very rare cases where that sense oligo is needed to counter a developing adverse effect in the patient, delivering that sense oligo into the patient only requires about a minute, with distribution into the proper subcellular compartment of the patient's cells occurring within an hour.

Appendix

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1. Scientific advances underlying new precision drugs

In 1944 Avery, McCarty, and MacLeod demonstrated that DNA carries the genetic information of cells. In 1950 Chargaff discovered that DNA has a special ratio of components wherein number of Adenines equal number of Thymines and number of Guanines equal number of Cytosines (A:T; G:C). In 1952 Rosalind Franklin carried out x-ray diffraction studies which indicated that DNA has a helical structure.

Building on Chargaff's A:T and G:C discovery, and Franklin's finding that DNA has a helical structure, in 1953 Watson and Crick succeeded in elucidating the detailed molecular structure of that helical DNA, and from that structure they deduced the molecular mechanism by which DNA carries its information, and can replicate that information, and how DNA can utilize the genetic information it contains to generate tens of thousands of RNA intermediates used for specifying the structures of

each of the proteins of the body.

The above advances led during the 1950s, 1960s, and 1970s to a host of key discoveries about genes, their functions, and their control. This, in turn, led to a deep understanding of genetics, embryology, evolution, and multiple other areas of biology - and gave rise to the new field of molecular biology.

2. The long journey to a new era in drug development

Based on the foundation afforded by the many DNA and RNA-related scientific discoveries beginning in 1953, in 1978 three research groups
each independently published their own distinct versions of a revolutionary new strategy for modulating the function of any selected gene by using compounds now known as "**antisense oligos**" (called **"antisense"** because they bind the **sense** strand of a targeted RNA, and **"oligo"** because they contain about 15 to 30 genetic letters in a sequence exactly complementary to the sense sequence in the targeted RNA). Those pioneering groups were:

Summerton* (myself**)** and Bartlett at Berkeley;

Miller and Ts'o at Johns Hopkins; and,

Zamecnik and Stephenson at Harvard.

* Note that in 1973 (the year I completed my Ph.D. in Biochemistry) I submitted to the Journal of Theoretical Biology a description of the antisense therapeutics strategy which I had first conceived of in 1969 (during a

seminar by B. R. Baker on active-site-directed irreversible enzyme inhibitors), but that paper was rejected because a reviewer judged the strategy to be just a "pipe dream". However, after carrying out proof-of-principle studies on the antisense strategy while a postdoctoral fellow at Berkeley, in 1978 I resubmitted a revised version of my 1973 paper - now including the results from my proof-of-principle studies at Berkeley. That revised version was then accepted by that same journal (and the original reviewer) and published in 1979 - with the original 1973 submission date included.

From those three pioneering publications in 1978 it was apparent to many scientists, and particularly pharmacologists, that this antisense therapeutics strategy offered tremendous promise as a means for quickly and efficiently devising precisely targeted therapeutics for most viral diseases, as well as for a host of other difficult-to-treat diseases such as cancers. Also in 1978 the first patent issued in this new antisense field (US Patent 4,123,610, issued to **Summerton** (me) & Bartlett, assigned to National Institutes of Health). In light of the great therapeutics promise of antisense oligos, in 1980 I founded the first antisense company, ANTIVIRALS, Inc. (now re-named "Serepta Therapeutics"), and 7 to 9 years later (1987 to 1989) four more antisense companies were founded (Genta, Hybridon, Gilead, & Isis). Also by the late 1980s most major pharmaceutical companies were heavily invested in this antisense drug development strategy - via both in-house programs and major deals with the startup antisense companies.

However, by 1993 it was becoming clear to most scientists in the antisense field (except those blinded by business considerations) that there was a huge problem that had to be solved before antisense oligos could serve as effective therapeutics. The problem was that after more than a decade of massive investment and effort, no one had yet achieved safe and efficient delivery of antisense oligos into the proper subcellular compartment in cells in vivo (ie., within living animals, including humans).

Wide recognition of that in vivo delivery challenge motivated hundreds of scientists around the world to embark on intense many-year efforts to solve that delivery problem. While those efforts led to development of multiple antisense delivery technologies, including 5 developed by my companies (ANTIVIRALS, Inc. and my 1997 spinoff company "GENE TOOLS, LLC"), nonetheless, to date none of those antisense delivery technologies have proven to be adequately safe nor adequately efficient for broad therapeutic applications. As a consequence, by about 2005 nearly all major drug companies and most researchers had abandoned their programs to develop antisense therapeutics because of that intractable in vivo delivery problem.

In contrast, I have continued efforts to achieve safe and efficient in vivo delivery of antisense oligos. Since 1993 I have led the development of 5 different antisense delivery systems, each better than the previous one - but none of my delivery systems, and none of everyone else's delivery systems, has yet proven adequately safe or efficient for broad therapeutic use. While there are a few special applications (eg., muscular dystrophy where

the affected muscle cells are inherently leaky) where a small amount of antisense oligo can be delivered into the proper compartment of a patient's cells without the use of a delivery system, nonetheless, it is clear the vast majority of potential applications of antisense therapeutics will remain in limbo until someone achieves a safe and efficient in vivo delivery system.

There was a further serious problem in that in 2010 the key patent expired on by far the best antisense structural type (my Morpholinos, see: http://en.wikipedia.org/wiki/Morpholino and Current Topics in Medicinal Chemistry ***7***: 651 (2007)). Expiration of this patent essentially assured that conventional pharmaceutical companies will not be interested in developing an antisense therapeutic of that structural type - unless some novel component can be patented. Otherwise companies cannot recoup the huge costs of clinical trials and regulatory approval inherent in our drug regulatory system.

Because of this expiration of the key patent, and even more so because of the lack of a safe and efficient in vivo delivery system, by about 2012 interest in the antisense therapeutics concept had declined to nearly zero in both the pharmaceutical industry and the medical research community.

In contrast, for basic biological research in a diverse range of research areas the use of custom antisense oligos as research tools (see: www.gene-tools.com) has remained robust worldwide because such antisense oligos allow a researcher to selectively modulate the function of a given gene in a couple of days at a cost of only $400 for a

custom antisense oligo - where before the advent of antisense oligos that same experimental study would have taken many months to a year or more and cost tens of thousands of dollars (if it could have been done at all).

While my company, GENE TOOLS, LLC, had continued to spend time and effort working to develop a safe and efficient in vivo delivery system, by 2013 it appeared that the demise of the antisense therapeutics concept was imminent unless a successful effort was made to finally solve the theretofore intractable in vivo delivery challenge. Since I probably have appreciably more experience (and more successes) than anyone else in developing antisense delivery systems, in 2013 GENE TOOLS began a substantially increased effort to develop a safe and efficient in vivo delivery system. This entailed adding a number of research scientists to our staff to focus on the synthetic work, plus another research scientist to focus largely on the substantial amount of cell culture and mouse studies required for this project. Further, I am also now focusing much of my time designing and synthesizing the key elements being incorporated into the many variations required for optimization of this new and novel delivery system.

After several years of substantial investment, this increased effort appears to be finally bringing us to our goal of a safe, efficient, and affordable in vivo delivery system. Specifically, early experimental results with individual components of our latest (6th) delivery system indicate we have successfully identified <u>all</u> of the complex challenges involved in moving a Morpholino oligo from the blood stream of a living animal to the cytosol/nuclear compartment of the animal's cells using safe, efficient

delivery components - suggesting that we can indeed construct a delivery system which achieves the long-sought goals of safe, efficient, affordable, and broadly applicable in vivo delivery in animals (including humans) - without compromising the exquisite sequence specificity inherent in the Morpholino antisense structural type.

Thus, I expect that in a few months GENE TOOLS will begin incorporating this latest in vivo delivery system into our custom antisense oligos, and begin routinely providing these delivery-enabled Morpholinos to the hundreds of research organizations which GENE TOOLS regularly supplies worldwide.

Once our preliminary antisense delivery results are confirmed for the full set of all the components of the new delivery system, and independently confirmed in mice, I expect these upcoming technological advances in the drug design field will this year (2015) make it possible to easily, cheaply, and quickly devise new affordable breakthrough drugs for a host of currently un-treatable or poorly-treatable diseases and conditions. This includes drugs suitable for affordably treating diseases and conditions present in only a few patients, and even in a single patient (ie., personalized medicine).

Design and synthesis of such breakthrough drugs will be remarkably similar to the design and synthesis of the one hundred to three hundred custom Morpholino antisense oligos which GENE TOOLS designs, produces, and ships each week to our research-scientist customers around the world - where each such Morpholino oligo is targeted against a different gene transcript specified by the customer (see: www.gene-tools.com). The key

difference will be the extra step of adding our new in vivo delivery components to those Morpholinos.

3. Risk-reduction method for antisense drugs

By the early 1990s the antisense field was reaching a reasonable level of maturity (excepting for a lack of safe and efficient in vivo delivery) and the focus was shifting from devising new antisense structural types to devising ways to confirm antisense activity in biological systems. To this end, two related methods were developed to assess the efficacy & specificity and control the activity of an antisense oligo. Both methods exploit Watson/Crick pairing between complementary sequences to halt the activity of the antisense oligo.

Both methods entail treating cells with the antisense oligo and incubating a sufficient time to allow depletion of the target protein (or generate some other desired activity). Then in order to halt the activity of the antisense oligo and thereby provide information on that antisense oligo's efficacy and specificity, the cells were treated with one of the following types of research tools:

a) **RNA transcript containing the targeted sense sequence complementary to the antisense oligo** added in sufficient quantity to tie up the available antisense oligo, plus additional RNA transcript for renewed production of the target protein (or other activity); and,
b) **sense oligo complementary to the antisense oligo** added to bind the antisense oligo and render it inactive - thereby allowing renewed production of the target protein (or other activity) from newly synthesized RNA

transcripts.

Since the early 1990s these commonly-used research tools to block the antisense oligo have been referred to by a variety of names, including:

rescue agents;
decoy agents;
sense oligos; and,
inverse complement oligos.

In **2002** Rusconi, Sullenger, and coworkers reported use of such Watson/Crick pairing between complementary oligos to halt the therapeutic activity of one of the oligos (Nature **419**, 90 (2002)). More specifically, they developed a modified oligonucleotide having a specific therapeutic activity. They then provided the complementary modified oligonucleotide (which they named the **"perfect antidote"**) which could be added if and when it was desired to halt or reduce the activity of the therapeutic oligo.

I believe this was the first reported case wherein this research strategy (long used in many research laboratories) of using a sense oligo for blocking the antisense oligo was applied for the express purpose of halting or reducing the biological activity of an oligonucleotide being used for a therapeutic purpose. In their summation of this work Rusconi, Sullenger, and coworkers stated: "This generalizable strategy for rationally designing a drug-antidote pair thus opens up the way for developing safer regulatable therapeutics".
In separate commentary on that work (Nature **419**, 23 (2002)) Tuddenham noted: "... the work of Rusconi et al shows how one RNA molecule can have an active role as a

drug, and can store the information required to make its own **perfect antidote**."

In **2006** this same research group published their first-in-human results with this ground-breaking combination of a therapeutic oligonucleotide drug administered to humans and subsequently its complementary antidote oligo administered to halt or reduce the biological activity of the therapeutic oligo. (Circulation **114**, 2490 (2006)).

In **2008** (with priority dating to **2007**) Monia, Siwkowski, and Zhang filed US Patent Application number 12/740,974, which issued in **2013** as US Patent 8,389,488 B2. That patent lays claim to virtually **all** methods wherein a therapeutic oligo is administered to cells or animals (including humans) and subsequently a complementary antidote oligo is administered to halt or reduce the biological activity of the therapeutic oligo.

However, that **2013** issued patent is clearly invalid because its Specification egregiously fails to meet two key statutory requirements for US Patent Applications.

1) The Specification must distinguish the invention (**priority dating only back to 2007)** from earlier inventions and from the prior art.

   This patent is clearly invalid because the Specification fails to distinguish the alleged invention from the other virtually identical technologies widely used by the scientific community for multiple years prior to the priority date of the patent application, and the Specification fails to disclose the nearly two decades of published prior art - art which is virtually identical to the

claimed invention and so renders their alleged "invention" entirely obvious. More important, their claims clearly read on a great deal of that prior art, including the **2002** publication by Rusconi, and particularly the **2006** publication demonstrating use of the **"perfect antidote"** in humans.

2) The Specification must particularly point out the part to which the improvement relates.

The patent is clearly invalid because the claimed invention does not constitute any improvement over the long-used and widely-published prior art entailing the use of a therapeutic oligo (eg., an antisense oligo) and subsequent addition of a complementary oligo (antidote oligo) to

block or decrease the biological activity of the therapeutic oligo.

In light of the extensive and long-available prior art, and the fatal flaws in the sole patent in this area, there appears to be no valid legal bar to the risk-reduction strategy to be used in this Right-To-Live Demonstration Project.