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World's first and only Safe and effective

Allergy Vaccine for Poison Oak (PO) & Poison Ivy (PI)

Investment opportunity

Wanted: Investors, entrepreneurs, developers to help us commercialize the world's first and only allergy vaccine to safely induce tolerance to PI and (we expect) highly cross-reactive PO

The Scientific proposal:

National need for an effective allergy vaccine for PI/PO: Poison ivy (PI), found east of the Continental Divide, and its highly cross-reactive cousin, poison oak (PO), found west of the Divide, are the most common causes of allergic contact dermatitis in the United States (US). Half of Americans will develop a rash from casual environmental contact at some point during their daily life and 80-90% will become clinically sensitized with higher levels of exposure (2). In a 2006 general review of Toxicodendron dermatitis (3) Gladman points out that even 20% of Americans living in urban environments experience clinical allergic contact dermatitis from PO/PI, that allergy to PO/PI causes 10% of all US Forest Service lost-time injuries, and that approximately one third of forestry workers in California, Oregon, and Washington are disabled by poison oak dermatitis each season. During severe fire seasons in the western United States up to 25% of U. S. Forest Service firefighters must be removed from duty because of this condition (4). In the late 1990's the cost of treating occupational allergic contact dermatitis from PO/PI consumed 1% of the State of California's entire yearly workers' compensation budget (5).

Other allergy vaccines were marketed for PI and PO prior to 1994, when the FDA began to require proof of efficacy as well as proof of safety and no manufacturer of a previously licensed vaccine submitted efficacy data. Reviewers in 2016 (15) and again in 2019 (20) stressed the need for a better allergy vaccine.

As background terminology for potential investors, The allergens in PI and PO are chemicals called urushiols, molecules side chains of 15 carbon atoms in PI and 17 carbon atoms in PO. Each is found in nature in four different forms, with zero, one, two or three double bonds (another term for unsaturated bonds) near the tail of those carbon side chains.

A safe and effective vaccine with an FDA-approved pathway to biologics licensure: I'd been impressed that while the older PI vaccines generally failed to induce total tolerance they often allowed severely allergic patients with occupational or other unavoidable exposures to reduce their need for prednisone. For this reason and in collaboration with Prof. Catherine Yang, then chair of chemistry and biochemistry at nearby Rowan University, I offered to make a vaccine from locally growing PI for a severely allergic occupationally exposed patient. We developed a quantitative version of a previously standardized patch test, to measure pre-treatment sensitivity and response to treatment (Tx). We took two shortcuts from previous production methods to make it easier to make in small volumes of vaccine in an ordinary chemistry laboratory. We were pleasantly surprised to find that these shortcuts, which we subsequently patented, gave us the world's first and to this date only safe and effective allergy vaccine for the most common cause of allergic contact dermatitis in North America (44). We'd discovered Vaccine Delivery by Precipitation (VDBP) by injecting a water-insoluble vaccine dissolved in small volumes of ethanol into skeletal muscle, a tissue containing large amounts of available water in which the injected ethanol is rapidly diluted. As the ethanol vaccine vehicle is diluted, the urushiol it carries becomes insoluble and precipitates. The more rapidly the ethanol is diluted, the larger the number and smaller the size of the resulting urushiol particles. We serendipitously hit a sweet spot, depositing hundreds of thousands of particles in the size range of 0.5 to 5 microns diameter within which particles are very efficiently picked up by the naive dendritic antigen-presenting cells that continuously patrol all tissues of the body outside of the blood-brain barrier, and bring those particles of allergen to local and regional lymph nodes in which switching of immune system response takes place. With informed consent we offered the same treatment to other allergic patients for whom avoidance was either impossible or impractical. The most sensitive two of our first four patients achieved tolerance with our initial formulation and dosing schedule. We

modified both formulation and treatment dose on the basis of accumulating experience, achieving a 90% response rate with our most effective formulations and doses. A small number of patients with suboptimal responses to all treatment doses requested retreatment, and 100% of these achieved tolerance with a single booster of our most effective formulation and dose. We found no correlation between clinical severity and pre-Tx patch test sensitivity but a 100% correlation between a 10-fold or greater post-Tx decrease in patch test reactivity and a durable clinical response to Tx (1). This contrasted with a no-greater-than 2-fold variation in patch test response in either absence of Tx or failure of Tx.

We failed to qualify for NIH SBIR pre-clinical funding because we do not have the capability to demonstrate the molecular mechanism we attribute to VDBP. This proof of mechanism is NOT required by the FDA, however, for allergenic products derived from natural source materials. In a 2020 pre-IND meeting the FDA approved our requested pathway to regulatory approval. Their ONLY requirements are that we: 1) standardize methods for vaccine production and packaging, 2) propose and subsequently adhere to vaccine lot consistency limits for both total urushiol and content of whichever group of congeners predominate in the formulations we choose to develop, 3) make all vaccines for future human use in compliance with standard pharmaceutical good manufacturing practices (GMP), and 4) achieve similar clinical trial safety and efficacy outcomes to those we encountered with immunologically identical vaccines our published human proof-of-concept experience (1).

Our clinical trial vaccines will be chemically and immunologically identical to the most effective vaccines used in our human proof-of-concept experience except for difference in congener ratio. Any resuling difference in potency will be adjusted in dose-ranging Phase 1 clinical trials. With this dose adjustment we see no reason not to expect a similar safety/efficacy profile to our human proof-of-concept experience, which will qualify for licensure for commercial sale.

Limited data from the 1970's and 1980's suggests that the polyunsaturated congeners (2 and 3 unsaturated bonds) are more allergenic than the others but they are also likely to be less stable and have shorter shelf life stability in storage. As discussed below, the vaccines we choose to take to clinical trial may have different relative fractions of the 4 congeners than the vaccines we used in our human proof-of-concept experience but they will otherwise be chemically identical. Phase 1 dose ranging studies should allow us to compensate for any resulting differences in net allergenicity, with the result that the vaccines to be used in Phase 2 pivotal clinical trials will be allergenically identical to the vaccines used in our human proof-of-concept experience. As such we can reasonably and reliably expect similar safety and efficacy outcomes on those pivotal clinical trials and that upon completion of those clinical trials the vaccines will be approved for commercial sale.

The cost to replicate the hand-made vaccines we used in our human proof-of-concept experience would be thousands of dollars per course of treatment. We assembled the following team to develop efficient and reliable agricultural and laboratory processes to produce safe and effective vaccines at commercial scale that predictably meet regulatory requirements for lot-to-lot consistency, at a production cost per course of treatment in the low tens of dollars. ***Our team comprises:***

Robert Coifman, M. D., (myself) the practicing allergist who serendipitously discovered Vaccine Delivery by Precipitation (VDBP), patented it together with my chemistry partner Prof. Catherine Yang, and assembled the rest of the team to make a GMP verison of the vaccine with the lot-to-lot and year-to-year consistency of content needed to achieve and maintain regulatory approval.

Catherine Yang Ph. D. was chair of the Department of Chemistry and Biochemistry at Rowan University in New Jersey where she oversaw the preparation of the vaccines used in the published series. She is currently Vice President of Academic Affairs and Associate Dean of Medical Education at California Northstate University (CNSU), a private medical university near Sacramento CA. She will perform urushiol assays for the vaccine development and in subsequent commercial manufacture in a biotechnology incubator facility established by her university in which faculty can set up and conduct small biotech businesses.

Mel Kornbluh is a local entrepreneur who built his family soda syrup business, Vineland Syrup, Inc., into a national specialty contract beverage and condiment manufacturer and the world's largest volume manufacturer of another FDA-regulated liquid sterile product, glucose tolerance-testing beverage. He also built his hobby

of bicycle touring into Tandems East, a nationally leading manufacturer of high end precision tandem bicycles. Mel will serve as CFO and bring his expertise in the implementation of cost-effective precision manufacturing processes and the development and operation of successful small businesses to this endeavor.

Eric Feerst is a retired NJ DEP lab chief currently working as head of quality control and regulatory affairs at Vineland Syrup Inc. He will be performing the same functions and also serve as manager of biological and chemical processes for the current project.

Merlin Weaver is an established Controlled Environment Agriculture (CEA) grower in Pittsgrove NJ. The project will lease space and facilities at his operation. He will direct the application of principles of agricultural science to the efficient cultivation of PI and PO and his staff will provide crop and facility maintenance.

Millan Bhatt is the owner of Molecular Pharma Group, a USP 503b sterile compounding pharmacy in New Providence, NJ. Millan will perform sterile packaging of clinical trial and initial lot vaccines for commercial sale. He will have the option to increase his own production capacity or outsource sterile packaging

Scott Oneto is a University of California Cooperative Extension Farm Advisor and the senior weed scientist at the University of California at Davis College of Agriculture. He will coordinate the collection of naturally growing PO and PO seeds as needed for the program and also serve as a consultant.

Pre-clinical R&D:

Genetic selection of plants to propagate: The ratio of urushiol congeners in the leaves of each individual PI or PO plant is genetically determined and is constant both for the life of the plant and in any progeny asexually cloned from that plant (personal communication, Prof. John Jelesko, College of Agriculture, Virginia Tech). We will (initially) germinate 100 seeds of each of PI and PO from a variety of locations, sample their seedlings for genetically determined urushiol congener distribution, and look for healthy, rapidly growing plants with high total urushiol content and urushiol congener distribution patterns that are both predominantly polyunsaturated (more allergenic but less stable in storage) and predominantly unsaturated and mono-unsaturated (more stable but less allergenic). We will look for multiple genetic strains (individual plants) with each of these congener distribution patterns to give us the resilience of genetic diversity in case we encounter plant diseases at any point in the future.

Germination of seeds: Seeds of PI and PO are normally spread by birds that eat the berries. Only 5-10% of seeds will germinate if planted without either passing through the digestive tract of a bird or having a laboratory treatment that replicates the same effect. Prof. Jelesko developed such a bird-equivalent seed preparation protocol (52). He gave us his 2021 update, with which he achieves gemination rates of 80-90%. We will use his protocol for seed germination.

Cloning of selected plants: The experienced growers on our team, Merlin and Scott, both have experience with standard agricultural methods for plant cloning. They will apply these to vines of naturally growing PI and PO to have optimized cloning protocols by the time.

Optimization of greenhouse cultivation conditions: PI and PO will be grown in a 2,880 sq ft greenhouse to be assembled from a commercially available kit in leased space at Merlin's operation, where routine greenhouse and cultivar maintenance can be contracted to his staff. The greenhouse will be equipped with a fully automatic environmental control system, a 630 place hydroponic nutrition system for mature plants, and additional space for germination, cloning and cultivation of seedlings. It will have supplemental LED lighting and a carbon dioxide generator to maintain the elevated CO2 levels associated with increased growth of PI (23). Nutrition and environmental conditions will be optimized according to known agricultural principles for proliferation of leafy green plants.

Conversion of leaves to vaccines: The single most important factor for urushiol stability is aggressive removal of even trace amounts of water. Fresh leaves of PI are 2/3 water by weight, PO possibly slightly less. The water content of fresh leaves can be removed without affecting antigenicity by drying at 50 deg C in a

forced air circulating microbiological incubator repurposed as a drying oven. Ethanol extracts of leaves dried in this manner and maintained under aggressive desiccation retained undiminished allergenicity for one year even when stored in sunlight and at room temperature (14). We plan to oven-dry freshly harvested leaves, extract their urushiol with ethanol and concentrate the resulting extracts in a modular building adjacent to the above R&D greenhouse.

We determined in our human proof-of-concept experience that our most effective urushiol vaccine is also the least costly to produce, a simple, unpurified, concentrated ethanol extract of oven-dried leaves. Crude extracts with unidentified constituents are not a problem for the FDA in allergenic products derived from natural source materials, as long as source materials and methods of preparation are the same in commercial lots as in the clinical trial vaccines that generate initial safety data. All but one of our human proof-of-concept vaccine formulations contained crude ethanol extracts of fresh leaves and none of these were associated with significant adverse effects.

We will standardize protocols to vacuum-concentrate the crude dried leaf ethanol extracts to slightly greater than our target vaccine concentration of 100 mg / ml. Assays of the urushiol content of these concentrates will let us dilute each such batch with exactly enough ethanol to achieve our target concentration for GMP packaging as urushiol vaccine. We will perform vacuum concentration on site to keep the volumes of flammable solvent that must be shipped to Millan in New Providence NJ will be below the thresholds that trigger Hazmat shipping requirements.

Shelf life stability testing will be performed with non-GMP vaccines made from naturally growing PI and PO so we can begin these studies before we have enough greenhouse-grown crops to harvest. Preliminary harvests of naturally growing PI and PO will be used to determine an optimal vol ethanol to wt dried leaf extraction ratio. Larger harvests for shelf life stability studies will be oven-dried, extracted at this ratio, concentrated and rediluted to our target concentration of 100 mg urushiol pr ml and shipped to Millan for filter sterilization, desiccation, and vial-filling in an atmosphere of dry nitrogen.

We plan to track the shelf-life stability of total urushiol and each individual congener of both PI and PO under the following conditions, chosen to minimize our total cost to provide product to purchasers and end users. We will compare shelf life stability of vaccines stored at 5 deg and 25 deg C. If they are equal that data will support our asking the FDA to allow storage without refrigeration and unrefrigerated shipment to buyers in other than hot weather. We plan to compare the above stabilities with those of vaccines subjected to heat shock consisting of two weeks at each of 40 deg and 50 deg C before storage at either 5 deg or 25 deg. C. If desiccated, drv nitrogen-packaged vaccines tolerate 2 weeks of heat shock at 40 deg C without either immediate degradation or accelerated long term degradation we can ask the FDA to permit unrefrigerated shipping to most of the country most of the year. If they tolerate 2 weeks of heat shock att 50 deg C without immediate or long term degradation we can ask the FDA to allow unrefrigerated shipping even to Arizona in summer, at least for now.

Our ***Choice of vaccines to bring to clinical trial*** will depend on both the congener distribution patterns we encounter in high urushiol content, rapidly proliferating genetic strains of plants and on the relative shelf life storage stability of the various congeners in vaccines packaged under optimal desiccation. If the shelf life stability of polyunsaturated congeners under optimal packaging conditions of is as good as that of unsaturated and monounsaturated congeners, we'll want to go to clinical trial with vaccines made from plant strains relatively high in polyunsaturated congeners. If polyunsaturated congeners have relatively and absolutely poor shelf life stability, we may want to go to clinical trial from genetic strains that produce relatively little polyunsaturated congener, if we encounter rapidly growing plants with these congener production patterns. The FDA invited us to request what would now be a third pre-IND conference when we have both shelf life congener stability data and the congener distribution data of the strains we've been able to propagate, to discuss what the FDA would like to see in the way of clinical trials.

The previously licensed urushiol vaccine with the largest market share was a mix of extracts of both PI and PO. The two urushiols are sufficiently cross-reactive to make it reasonably likely that a single plant source vaccine will be "non-inferior" (an FDA definition) and much less costly to produce than a vaccine that requires greenhouse cultivation, leaf drying, ethanol extraction, concentration and all the associated urushiol assays

from two separately maintained crops.

We therefore plan to produce two clinical trial vaccine stocks, one containing the C-15 (15 carbon chain) urushiols of PI and the other containing the C-17 urushiols of PO. Following Phase 1 dose-ranging studies with the two separate vaccines we plan Phase 2 pivotal clinical trials of three vaccines, one containing only the urushiols of PI, the second containing only the urushiols of PO, and the third containing equal quantities of both. The same 3 vaccines will be studied in populations allergic and exposed to PI east of the Continental Divide, and populations allergic and exposed to PO in the crier climate of the West. If one or both single plant source vaccines proves non-inferior to both of the other vaccines in both study populations we will seek labeling to treat both allergies with what we will by that time have determined to be the least costly-to-produce single plant source vaccine.

Prof. Yang's economical ***Urushiol assay:*** Our process of vaccine development will require thousands of quantitative assays for urushiol content and congener distribution, we estimate close to 2000 per year. Standard methods of assay, gas chromatography + mass spectrometry (GC-MS) and liquid chromatography + mass spectrometry (LC-MS) are expansive because pure urushiols are unstable and require chemical conversion to stable derivatives for quantitative assay, a process called "derivatization.". Prof. Yang developed a shortcut that delivers 95% accuracy without loss of precision or reproducibility (performance standards acceptable by the FDA) that does not require derivatization. The lowest cost quote we could find for quantitative assay of urushiol content and congener distribution with derivatization was $800 per assay. Prof. Yang can perform her assay, with a 3 year flat rate contract for 2000 +/- 20% assays per year using dedicated equipment, at a cost for each assay of $25.

Prof. Yang's assay is as old as our patent for urushiol VDBP, which we filed in 2010, but it was never published or otherwise reported in the public domain. It thus remains eligible for 20 years of patent protection, for which we plan to start the clock by filing when we have the funding to proceed with vaccine development. While our patent on VDBP urushiol vaccine expires in 2030, patent protection on a 97% reduction in the cost of the thousands of assays needed to make it will give us a functional monopoly on commercial vaccine production for 20 years from the date of filing.

Choosing clinical trial treatment schedules for maximum market access: The FDA treats clinical trials as a closely monitored exact preplay of what the applicant is seeking approval to then market to the public without a need for continuing clinical trial-level scrutiny. If we want our vaccine to have the accessibility of administration in pharmacist-supervised retail pharmacies, nurse-supervised employer workplace clinics and other settings that lack physician supervision, we'll need to have clinical trial dosing schedules with sufficiently benign adverse event profiles for the FDA to determine that physician supervision is not necessary.

Our human proof-of-concept experience confirmed that as is generally true for allergen immunotherapy, lower starting doses and more and smaller steps to achieve an effective treatment dose are associated with reduced frequency and severity of advese effects. The only adverse effects we encountered were swelling and tenderness at injection sites in patients traveling long distances for care and asked for rapid dose escalation to minimize the number of trips needed to complete treatment, and dermographism (hives provoked by scratching the skin) lasting 3 months and accompanied by an elevaed eosinophil count in a single patient (myself) treated with a highly purified vaccine at more than twice the highest dose we now plan to study, before we discovered that with either unpurified concentrated vaccines or purified concentrated vaccines to which crude unpurified extract had been added, doses that high were not necessary. We believe that clinical trial dosing schedules of 6 steps for doose ranging Phase 1 clinical trial recipients of cumuative urushiol treatment doses of 15 mg, 7 steps for recipients of cumulative doses of 25 mg and 8 steps for recipients of cumuative doses of 35 mg, should yield adverse event profiles sufficiently benign for the FDA to allow administration in retain pharmacies and other setting without direct physician supervision.

If this hypothesis turns out not to be correct, we'll be ablle to further slow our treatment schedue for the pivotal Phase 2 studies to follow and generate the data on which the FDA will make its decision.

Booster doses: We know from our human proof-of-concept experience that tolerance is lost at different times post treatment in different patients. We know from limited experience that patients who have lost tolerance

respond to retreatment but also that they again require mullti-step dosing to control their risk of acverse reactions. It would be desirable from both medical and business perspectives to validate the safety and efficacy of a one step booster dose, comprising a complete treatment dose o be given at one time, while the patiet retains his or her initial tolerance and does not require multi-step dosing. The proposed annual single-stepboosters can be given at a single encounter in either a single injection field on an arm or leg (likely to be more effective at induing tolerance but also more likely to cause injection site reactions), or in multiple locations (less likely to induce injection site reactions but possibly slightly less potent as an inducer of tolerance).

Organization and conduct of clinical trials:

The abbreviated clinical trial sequence for which the FDA gave us preliminary approval is sufficiently different from the standard workflow of commercial clinical research organizations that it may prove most expedient for me to personally organize them and solicit subinvestigators and clinical trial sites from the memberships of the two national allergy specialty societies. Their memberships include many allergists who already have clinical trial centers that they use for mostly pharmaceutical industry-sponsored studies. Team member Scott Oneto independently works with large employers with workforces occupationally exposed to PO. He advised us that some of these employers or consortia of these employers may want to sponsor and fund clinical trials for their exposed and allergic employees. These will be options if approved by both the FDA and the IRB. We do not expect the FDA to allow a principal investigator with an economic interest in the product to also host a clinical trial site because of potential conflict of interest.

If we are able to recruit an academic center as a clinical trial site we may be able to use its IRB for the entire study. Otherwise we will contract with a commercial IRB, preferably one familiar with clinical trials of allergy vaccines.

As noted above, it was one of the allergist members of the FDA's pre-IND meeting who proposed that we validate our proposed primary endpoint of a 10-fold or greater reduction in quantitative patch test reactivity by testing each clinical trial subject twice before and once after treatment. This will make each subject his or her own control, eliminate the need for placebo control stud arms, facilitate recruiting as every study subject will e treated with one or another active vaccine, and reduce study costs.

Currently proposed clinical trials are:

Phase 1: 10 subjects with each of 3 doses of the formulations of each of the 3 vaccines (PI, PO and mixed) that we plan to bring to clinical trial. Tentative doses are 15, 25 and 35 mg of single component vaccines and 20, 30 and 40 mg of mixed vaccine. If none of these doses replicate our human proof-of-concept safety/efficacy profile se can expand the range of study doses either up or down as needed. To thank clinical trial participants I'd like to offer whatever we determine to be our final treatment dose to any non-responders who initially received lower doses, and single booster doses to any subjects who fail to respond to a full treatment dose, with tracking of changes in quantitative patch test reactivity after each such additional treatment.

Phase 2: One, or, if the FDA requires, 2 comparisons of response of 30 subjects in the eastern US, allergic and exposed to PI, to allergy vaccines containing only the urushiols of PI, only the urushiols of PO and a mix of the two. Similarly one, or, if the FDA requires, 2 comparisons of response of 30 subjects in the western US, allergic and exp1osed to PO, to allergy vaccines containing only the urushiols of PI, only the urushiols of PO, and a mix of the two.

Trials of annual booster safety and efficacy: Options include beginning by offering single site boosters to recipients of Phase 1 vaccines at whichever of the 3 Phase 1 study doses we then decided to advance to Phase 2, and decide on the basis of tolerance whether to request FDA permission to offer the same treatment option, full dose at one setting but split between multiple injection fields, or to drop dose to ~50% of total initial Tx dose. That dose would still be slightly above the largest dose of the initial treatment schedule and has a reasonable likelihood of still being effective as an annual booster and would be worth exploring as a way to

achieve the safety of single visit boosters. Each clinical trial booster subject will have quantitative patch test sensitivity testing before and one month after booster dosing. A finding of no significant fall from post-initial-Tx patch test sensitivity and no boost after booster dosing will not adversely effect our request for FDA approval of annual boosters. A finding that treated subjects remain sufficiently tolerant to accept an effective annual booster dose at one time will validate that management option as a safe way to maintain tolerance with vaccine use in the general population, for whom patch testing before and after treatment is not possible.

Additional (limited) clinical trials to extend vaccine use life: Urushiol is not the only active ingredient of our vaccines. A highly purified concentrated urushiol vaccine did not work as well, by itself as when it was diluted with an equal volume of crude, unpurified ethanol extract. This demonstrated the role of an unidentified substance present in unpurified crude extract. This is not a problem under FDA regulations for allergenic products derived from natural source materials but it means that we'll have to confirm and validate use life by clinical trials in addition to urushiol stability. On the basis of our human proof-of-concept experience we'll want to conduct initial clinical trials with vaccine between 27 and 33 months old, which will give us an initial use life of 27 months from date of manufacture. Maintenance of a clinical trial vaccine supply within this age range will require ongoing greenhouse cultivation, harvesting and conversion to vaccine. We'll want to negotiate a process with the FDA by which limited studies with progressively older lots of vaccine will let us extend labeled use life.