The World's First and Only Safe and Effective Allergy Vaccine for Poison Ivy (PI) & Poison Oak (PO): Scientific Proposal

(updated 10/27/24)

Wanted: Investors to help commercialize the world's first and only safe and effective allergy vaccine to induce tolerance to PI and (we expect) highly cross-reactive PO

CAPSULE SUMMARY OF VACCINE DEVELOPMENT

The Food Drug and Cosmetic act allows an individual physician to make allergenic products for his own patients without regulatory oversight. This let us both make the vaccine in the first place and offer it to others with changes in dose and formulation based on accumulating experience. Our most effective doses and formulations were 90% effective on initial treatment. 100% of those patients with an unsatisfactory initial response who accepted our offer of a single booster dose responded, and we had no serious adverse effects.

We took a set of shortcuts from the methods by which previous PO & PI allergy vaccines had been made, to let us make a small quantity of a home-made vaccine for a single highly allergic patient. These shortcuts unexpectedly resulted in Vaccine Delivery by Precipitation (VDBP), a new and potent way to deliver antigens to the immune system, and with it the world's first successful induction of durable, measurable and clinically relevant real world immunological tolerance to the urushiols of PI &/or PO in a previously sensitized individual.

How VDBP works: Urushiol is soluble in ethanol but insoluble in water. The vaccine is an unpurified solution of urushiol (together with other ethanol-soluble substances present in oven-dried leaves) in ethanol. Concentration allows effective treatment doses to be dissolved in small enough volumes for patient tolerance without significant discomfort, to avoid tissue injury, and to be diluted by the water content of the muscle into which it's injected at a rate at which the dissolved urushiol becomes insoluble and precipitates into hundreds of thousands of particles in the 0.5 to 5 micron size range in which particles are efficiently taken 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 (1)

If we put a price tag on our professional time our hand-made vaccines cost thousands of dollars per course of treatment. To make our vaccine commercially successful we developed a commercial scale production technology to make the vaccine at a cost per initial course of treatment or annual booster of approx. $30-$60, which our economic analysis suggests that we can maximize income by selling at a wholesale price of approx. $300, to treat the tens of millions of Americans expected to want the vaccine as soon as it's validated and available.

A NATIONAL NEED FOR AN EFFECTIVE 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 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 PI/PO, that

allergy to PI/PO causes 10% of all U.S. 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 1990s the cost of treating occupational allergic contact dermatitis from PI/PO 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 (6) and again in 2019 (7) stressed the need for a better allergy vaccine.

WHY & HOW WE PLAN TO ACHIEVE LOT-TO-LOT VACCINE CONSISTENCY AND GMP COMPLIANCE

The allergens in PI and PO are chemicals called urushiols, molecules consisting of a common ring structure with 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. The ratios of the different congeners produced by each individual plant is genetically determined. Because of suggestions in the medical literature that different congeners differ in their antigenicity, both the FDA and principles of scientific integrity require lot-to-lot and year-to-year consistency in both total urushiol content and congener distribution.

We will populate our cultivation greenhouse with clones of plants selected for homogeneity of their genetically determined congener distribution patterns This will build the lot-to-lot and year-to-year consistency required by both medical and regulatory standards into the crop from which we make our vaccine.

We will dry freshly harvested leaves to remove their 2/3 by wt content of water, which if left in place complicates vaccine production and facilitates urushiol biodegradation (8). Urushiol will be extracted from dried leaves with ethanol and the resulting crude ethanol extract concentrated to a urushiol content slightly greater than the 100 mg / ml at which strength it will be used as a vaccine. Not only is concentrated crude ethanol extract less expensive to produce than purified urushiol at the same concentration, but the unpurified vaccine is more effective. It contains an unidentified substance that contributes to effectiveness but is lost in the process of purification. All of this is permitted under FDA rules for allergenic products made from natural source materials.

We will ship urushiol concentrate to team member Millan Bhatt’s Molecular Pharma Group FDA 503b compounding pharmacy in New Providence, NJ, where it will be filter-sterilized (ethanol does not satisfy the FDA’s requirements for terminal sterilization), assayed to determine the exact amount of dilution needed to precisely achieve our target concentration of 100 mg / ml, diluted to achieve that concentration and then aseptically packaged in multi-dose injection vials under desiccating conditions.

A SAFE & EFFECTIVE VACCINE WITH AN FDA-APPROVED PATHWAY TO BIOLOGICS LICENSURE

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 pre-Tx patch test sensitivity and either disease severity or response to Tx. However, there was a 100% correlation between a 10-fold or greater post-Tx decrease in patch test reactivity and a durable clinical response to Tx (9). This contrasted with a no-greater-than 2-fold variation in patch test response in either absence of Tx or failure of Tx.

We are not eligible for NIH SBIR pre-clinical funding because our chemistry team member, Prof. Catherine Yang, is now employed by a for-profit institution and her share of project work, setting up and performing urushiol assays, would exceed the SBIR program limit for % of grant-funded work that can be performed by a for-profit collaborating entity that isn't itself a small business. We are therefore seeking Round 1 private investor funding to validate the production strategy we designed for precise, cost-effective commercial scale vaccine manufacture and make clinical trial vaccine.

PRE-CLINICAL R&D

A highly purified urushiol vaccine was less effective than the same vaccine when mixed with a small amount of crude, unpurified ethanol leaf extract. This tells us that an unidentified substance or combination of substances present in crude, unpurified extracts is important for optimal efficacy. The lack of significant adverse reactions to any of the vaccines we studied in our human proof-of-concept experience suggests that our decision to commercialize an unpurified formulation with superior efficacy does not carry a downside risk of increased adverse effects. Our vaccine will join the large majority of FDA-approved allergenic products made from natural source materials that require direct or indirect assays of known active pharmaceutical ingredients to achieve lot-to-lot and year-to-year consistency but for which the regulatory agency recognizes that identification and quantification of all components that might affect efficacy is typically impractical.

This summer (2024) hydroponic vegetable farmer team member Merlin Weaver is testing standard agricultural cloning methods identify a protocol to be used to populate our cultivation greenhouse when our assay to identify plants with the same or similar congener distribution pattern becomes operational. He is also monitoring plants with and without supplemental LED lighting to see if maintenance of a 16 hr illumination cycle will prevent the plants from going into their normal end-of-summer dormancy and give us an extended growing season.

Round 1 funding will allow Prof. Yang to set up her low-cost urushiol assay, or which we are preparing to file for patent protection. Her assay is semi-quantitative rather than quantitative but sufficiently precise and reproducible to meet regulatory standards as a measure of lot-to-lot consistency. Its advantage compared to a quantitative molecular assay is its cost at commercial volume of $50 per assay while the cost of the quantitative molecular assay is ~$800.

When her assay becomes available we will begin shelf life stability studies for vaccine made from naturally growing PI under different conditions of packaging and storage. We will compare storage at room temperature with storage under refrigeration. If the major congeners in our vaccine are stable at room temperature that data will let us ask the FDA to permit room temperature storage, reducing our costs to provide vaccine to end users. We will study the effect on immediate congener stability and subsequent shelf life stability of 14 days at each of 40 and 50 deg C before return to either room temperature or with refrigeration. If there is no adverse effect of 14 days at 40 deg C we can request FDA approval to ship without refrigeration to most US destinations most of the year. If there is no adverse effect of 14 days at 50 deg C we can request approval to ship without refrigeration to all US destinations at any time of year, again reducing costs. We will perform the above sets of studies both with vaccine stored as crude ethanol extract of dried leaves concentrated to slightly more than 100 mg / ml and diluted to that concentration before packaging, and as the same vaccine with the solvent evaporated under vacuum at refrigerated temperature, to see if solvent removal by evaporation increases congener shelf life stability. If solvent evaporation significantly improves shelf life stability within the 12 months for which we'll have stability data before we have to decide on a formulation to take to clinical trial, we will package solvent-evaporated vaccine for clinical trials and subsequent commercial use. Span and Cooke, who in 1927 reported almost everything we now want to do with ethanol solutions of urushiol

except to inject it into muscle in the concentrated ethanol solutions needed to produce VDBP, reported that solvent-evaporated ethanol extracts redissolve readily upon reconstitution with ethanol (7). If solvent evaporation turns out to prolong shelf life but only after the first 12 months we will launch the vaccine with liquid dosage packaging and defer exploration of the business feasibility of trading the added costs of solvent evaporation and provision of filter-sterilized ethanol for redissolution and the user inconvenience and error risk of having to perform redissolution, against the benefits of a longer urushiol shelf life. If there is no difference in shelf life stability within 12 months post packaging it will probably be pragmatic to defer addressing this question until we see how the business is doing with packaging without solvent evaporation.

In our 2020 pre-IND meeting, the FDA approved a no-obstacles pathway to regulatory approval based on our human proof-of-concept experience. Their only requirements are that we:

1. Standardize methods for vaccine production and packaging,
2. Propose target levels and (for their approval) tolerance limits for total urushiol content and congener distribution, and
3. Make all vaccines intended for human use in compliance with Good Manufacturing Practices (GMP).

As previously noted we will build compliance with the lot-to-lot consistency requirement into our plant source by only populating our greenhouse with clones of plants for which the genetically determined congener distribution patterns are identical or nearly identical. While ethanol is functionally self-sterilizing it does not by itself meet FDA requirements for aseptic packaging. Both the vaccine and the ethanol to be used for final dilution will have to be passed into Milan's clean room through sterilizing filters before final assay, dilution to exactly 100 mg/ml, and packaging in injection vials either with or without solvent evaporation.

Further interventions we plan to study to increase productivity include:

1. Benefits of optimization of supplemental LED lighting, nutrition and environmental conditions according to known agricultural principles for proliferation of leafy green plants
2. Reducing ethanol to leaf extraction ratio, from the 9 ml / gram used by Spain and Cooke in 1927 to 5 and 3 ml / gram. If it yields close to the same urushiol extraction it will reduce all of extraction time, need for ethanol as a supply item, and volume of hazardous waste disposal.
3. Reducing leaf extraction time will only be practical after we confirm the efficacy of our current production protocol and launch commercial production with our current 7 days. This is because we cannot measure the extraction time of the unknown ingredient of the crude extract that confers adjuvant activity, with the consequence that vaccine prepared with shorter extraction times will have to be compared to that with 7-day extraction in additional small Phase 1 clinical trials.

CLINICAL TRIALS: The following are our clinical trial plans pending approval by the FDA, which offered to give us a second pre-IND meeting at no cost when we have final specifications for the vaccine we plan to bring to clinical trial.

Choosing clinical trial treatment schedules for maximum marketability: The efficacy of our vaccine is a function of cumulative treatment dose. The frequency and severity of adverse effects, almost exclusively injection site reactions with a rare case of transient urticaria with eosinophilia, depends on starting dose, number of steps and dosage increments in the treatment schedule. We presently plan to compare treatment doses of 14, 23 and 32 mg in Phase 1 dose-ranging clinical trials. Our human proof-of-concept experience suggests that schedules of 5 steps for cumulative treatment doses of 14 mg of urushiol, 6 steps for cumulative doses of 23 mg and 7 steps for combative doses of 32 mg, should yield sufficiently benign adverse event profiles for the FDA to allow administration in retail pharmacies and other setting without direct physician supervision. If these schedules prove too fast, we can reduce the adverse reaction rate with a lower starting dose and an additional step or two to achieve the target cumulative dose.

We plan to offer a dose-tracking database to make it easy for patients to get accurate sequential doses anywhere in the U. S. If a complete cumulative target treatment dose has not been received within a consecutive 4-month period, the program can be written to repeat the last step or two before progressing, to compensate for the possibility of partial loss of tolerance because of the gap in treatment.

Validation of primary endpoint and no need for placebo control arms: The senior allergist on the FDA team that conducted our 2020 pre-IND meeting is the same person who pulled the previously licensed PI and PO vaccines from the market in 1994 when their sponsors failed to provide data confirming efficacy. He and his team were enthusiastic about the prospect of being able to license a safe and effective vaccine for these allergies and were generous in offering guidance through the regulatory process. They suggested a clinical trial design that will simultaneously validate our proposed primary endpoint (a 10-fold or greater reduction in sensitivity by our quantitative patch test) and eliminate the need to make some subjects placebo controls. Their suggestion was that we patch test every study subject twice before treatment and a third time after treatment. The difference in sensitivity between the two patch tests results without treatment, which in our human proof-of-concept experience has never been more than 2-fold, will serve each patient's personal placebo control against which to measure his or her change in sensitivity after treatment. In our human proof-of-concept series this endpoint had a 100% correlation with the induction of durable real world clinical tolerance. In our clinical trial design subjects will have sufficient follow-up of clinical response to confirm that this correlation still holds.

We achieved this outcome in 90% of patients treated with vaccines that were functionally identical to the dose and formulation we plan to bring to clinical trial. We offered booster doses to patients with unsatisfactory responses to natal treatment: 100% of the small number of unsatisfactory responders to this dose and formulation achieved tolerance following a single booster. With a pivotal clinical trial pathway that replicates our successful human proof-of-concept experience we do not foresee an investment risk of failure to achieve clinical trial objectives.

Booster doses: We know from our human proof-of-concept experience that tolerance is lost at different times post treatment in different individuals. We know from limited experience that patients who have totally lost tolerance respond to retreatment, but that they again require multi-step dosing to control their risk of injection-site reactions. We know that patients with less-than-satisfactory responses to initial treatment respond to one-step booster doses without adverse reactions. We did not see any human proof-of-concept responders to our most effective cumulative treatment doses of 16 to 23 mg lose tolerance in less than 13 months, though some lost tolerance by 2 years.

Maintaining approval for administration in retail pharmacies will depend on not having significant numbers of reactions that either a physician or a patient might perceive as needing medical care. require physician care. We will ask the FDA to authorize clinical trials of booster safety and efficacy 12-13 months after completing initial treatment as a basis to request approval to recommend and offer booster doses at 11–13-month intervals. We will plan a small (10-12 subject) safety study of one-step booster doses 12-13 months after completion of initial treatment in early clinical trial responders. Their adverse events profile will determine whether we perform 12-13-month pivotal booster safety/efficacy trials with one step or 2-step dosing schedulers. The dose-tracking database can then be configured to notify patients at 10, 11 and 12 months that it's time for their boosters. It will route patients who have not received boosters within 13 months after their most recent previous dose to repeat the initial vaccine sequence.

Organization and conduct of clinical trials: A biopharmaceutical VC company that invests in companies for which it becomes the manager of their clinical trials has expressed interest in becoming our clinical trial management company. Our clinical trial needs are sufficiently different from the drug trials that are the bread and butter of most contract clinical research organizations that a sampling of contract CROs whose names came up in a Google search for CROs that accept studies involving vaccines were uniformly uninterested in our clinical trial needs. Alternatively, interested allergists who already conduct contract clinical research in their practices or who might specifically be interested in participating in clinical trials of this vaccine, could be recruited through the two allergy specialty societies of which Dr. Coifman is

both a fellow and a past scientific committee chair. We are confident that if needed we can put together a clinical trial network for this project.

.

Team consultant 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.

Currently proposed clinical trial details:

Phase 1: 10 subjects will be treated with cumulative doses of each of 14, 23 and 32 mg of urushiol. A decision for which dose to bring to clinical trial will be based on adverse events profiles, the frequency of achieving our endpoint of a 10-fold or greater reduction in patch test sensitivity and the distribution of pre and post-treatment patch test reactivity scores. (In our human proof-of-concept experience there was no correlation between clinical sensitivity and absolute patch test sensitivity but clinically sensitive patients who were less sensitive by patch testing generally required larger treatment doses to achieve tolerance.)

We will only perform dose-ranging Phase 1 studies in centers east of the Continental Divide, where subjects will be exposed and allergic to PI.

Phase 2: Subject to biostatistician recommendation to test different numbers of subjects, we will test and treat 30 subjects exposed and allergic to PI at one or two centers east of the Continental Divide, where PI is the predominant source of urushiol exposure, and an equal number exposed and allergic to PO at one or two centers where PO predominates, in the drier climate of the West.

If the FDA allows, we'd like to offer a single booster dose to any clinical trial subject who fails to achieve our primary endpoint of a 10-fold or greater reduction in patch test sensitivity following initial treatment. All clinical trial subjects will be asked to report any recurrence of symptoms in a 1-10 severity scale setting their personal pre-treatment severity as level 10. Responders will be asked to return for follow-up patch testing 11-12 months following completion of initial treatment, at which time they will be offered boosters and invited to participate in a post-booster year of tracking with the added incentive of a voucher for another free booster in a participating retail pharmacy at that time (by which we expect the vaccine to be commercially available).

Trials of annual booster safety and efficacy: Depending on subject numbers requested by the FDA, we will invite a subset or all study subjects returning for 12-month follow-up patch tests to participate in a clinical trial of boosters. The current plan is to begin with boosters containing a complete cumulative initial treatment dose in a single step. If one-step boosters turn out to elicit significant injection site reactions, we will default to a two-step booster schedule.

We will want to repeat patch testing 2-4 weeks after completing booster treatment with the same requests for quarterly symptom reports and to return for another set of patch tests 12-13 months after receipt of a first annual booster. We may want to offer a second annual booster as an incentive to subjects to return for one-year post first annual booster patch tests.

Additional (limited) clinical trials to extend vaccine use life: Initial clinical trials will of necessity be performed with relatively new lots of vaccine. Urushiol is not the only active ingredient of our vaccines. We confirmed that an unidentified substance present in crude ethanol extracts contributes to vaccine efficacy but is lost in urushiol purification, as a highly purified urushiol was less effective than the same amount of unpurified urushiol. Mixing purified urushiol with additional crude extract restored its efficacy to that of a completely unpurified vaccine. We don't know what this substance is, which is not a problem under FDA regulations for allergenic products derived from natural source materials, but without being able to directly measure its own shelf life stability he only way we can validate extensions of vaccine use life is by clinical trial. We will negotiate with the FDA for what we hope will be small and inexpensive trials of increasingly older lots of vaccine.

Cross-efficacy of PI vaccine for PO highly likely but not 100%:

The urushiols of PI and PO are sufficiently cross-reactive that an effective vaccine for PI is likely to be equally effective for PO. Until it's confirmed in clinical trials, however, it cannot be guaranteed. In the unlikely event that our vaccine meets efficacy criteria for PI rot not for PO our plan would be to license it for PI alone, which is the source of the urushiol to which 80% of the U. S. population is exposed.

Income from sales for PI would more than cover costs to make a similar vaccine from PO to be cultivated under similar conditions. We can then make and validate a combination vaccine containing both PI and PO.

We thank you for your interest in this product and this project.

Robert E. Coifman, M.D.

REFERENCES

1. Xiang SD, Scholzen A, Minigo G, et al. Pathogen recognition and development of particulate vaccines: does size matter? Methods. 2006;40:1e9.
2. Epstein WL et al: Poison Oak Hyposensitization, Evaluation of Purified Urushiol. Arch Dermatol 1974 Mar;109(3):356-60.
3. Gladman AC: Toxicodendron Dermatitis: Poison Ivy, Oak, and Sumac. Wilderness and Environmental Medicine 2006; 17:120-128.
4. Oltman J, Hensler R. Poison oak/ivy and forestry workers. Clin Dermatol. 1986 Apr-Jun;4(2):213-6.
5. Epstein WL: Occupational Poison Ivy and Oak Dermatitis. Dermatol Clin. 1994 Jul;12(3):511-6. .
6. Pekovic DD Vaccine against Poison Ivy Induced Contact Dermatitis, A Lingering Scientific Challenge. Int J Vaccines Vaccine 2016; 2(1): 00023. DOI: 10.15406/ijvv.2016.02.00023.
7. Kim Y, Flamm A, ElSohly M, Kaplan DH et al: Poison Ivy, Oak, and Sumac Dermatitis: What Is Known and What Is New? Dermatitis. May/Jun 2019;30(3):183-190. Doi: 10.1097.
8. Spain WC & Cooke RA: Studies in Specific Hypersensitiveness XXVII. Dermatitis Venenata: Observations upon the Use Of a Modified Extract from Toxicodendron Radicans (L.). J Immunol. 1927; 13:93-112.
9. Coifman RE, Yang CF, Tolerance to poison ivy following vaccine delivery by precipitation, Annals of Allergy, Asthma and Immunology 2019(Mar);122:331-33