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

(updated 4/19/25)

Wanted: Investors to help commercialize the world's first and only immunotherapy antigen (allergy shot) proven in human patients to safely induce durable, measurable, real world immunological tolerance to poison ivy (PI) and (we expect) highly cross-reactive poison oak (PO)

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NOMENCLATURE: Antigenic products administered to induce tolerance were called allergy vaccines until the name, Vaccine, became divisive. To not alienate potential recipients because of negative associations with the word "vaccine" we will call them what vaccines are, "antigenic products administered for immunotherapy," "immunotherapy antigens," or, colloquially, "allergy shots."

CAPSULE SUMMARY OF FORMULATION DEVELOPMENT

The Food Drug and Cosmetic act allows physicians to make allergenic products from natural source materials for their own patients without regulatory oversight. This let us make our own allergy shots for a single highly allergic and occupationally exposed patient. To make it practical to make a small lot of treatment antigen without a closed sterile formulation facility we took a set of shortcuts from previous formulations. These unexpectedly resulted in Antigen Delivery by Precipitation (ADBP), a new and potent way to deliver antigens to the immune system. Instead of the partial relief we expected, our patient surprised us with the world's first successful induction of complete immunological tolerance in a previously sensitized human. We developed a patch test to measure sensitivity, offered the same treatment to others, and achieved tolerance in the most sensitive two of our first four patients. With dose and formulation changes guided by accumulating experience we achieved a 90% response to initial treatment with a 100% response of those with an unsatisfactory initial response to a single booster dose. We had no significant adverse effects.

How our ADBP allergy shots works Urushiol, the antigenic material made by PI and PO, is soluble in ethanol but insoluble in water. Our immunotherapy antigen is a concentrated, unpurified ethanol extract of oven-dried leaves. Drying removes water which biodegrades urushiol in solution. Concentration allows effective treatment doses to be given in small volumes of ethanol to minimize tissue irritation and discomfort. Unpurified extracts are not only less expensive than purified urushiol solutions, but also more effective and are permitted by FDA regulations for allergenic products derived from natural source materials.

Previous urushiol immunotherapy antigens were also unpurified extracts but dissolved in sterile vegetable oils and injected under the skin. The urushiol remained in the injected blobs of oil, and diffused into the surrounding tissue fluid one molecule at a time. In ADBP, the urushiol is dissolved in ethanol and injected into muscle, chosen as a target tissue because its high water content will quickly dilute small volumes of injected ethanol to non-irritating concentrations. As the ethanol is diluted by the water content of the muscle, the urushiol becomes insoluble and precipitates into clumps scattered through a volume of muscle surrounding the injection site. The faster the dilution, the larger the number and smaller the size of the urushiol clumps. Our shots worked where others had failed because we happened to achieve a dilution rate that deposited hundreds or thousands to millions of clumps of urushiol molecules in the 0.5 to 5 micron size range that are bite-sized snack food for naïve antigen-presenting cells (APCs). These are the wandering dendritic cells that patrol all body tissues outside of the blood-brain barrier, looking for interesting antigens to bring to draining lymph nodes for processing They pick up particles of different sizes by different molecular mechanisms. Macropiocytosis, the mechanism by which APCs pick up particles in this size range (1), for the first time delivered a strong enough signal to the immune system to flip its response to tolerance from an already established state of sensitization.

A NATIONAL NEED FOR AN EFFECTIVE TREATMENT FOR ALLERGY TO PI/PO:

Plants of the genus toxicodendron evolved in North America about 80 million years ago. They make urushiols to protect themselves against certain plant diseases. We humans are an invasive species on their turf and they treat us the way we treat invasive species on our turf.

PI, which predominates east of the Continental Divide, and its highly cross-reactive cousin, PO, which predominates in the drier climate of the West, are collectively the most common cause of allergic contact dermatitis in the United States (US). Eighty-five % of Americans will become sensitized with sufficient exposure and half of Americans will seek medical care for these allergies (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).

Half of all Americans, 185 million, will at some point seek medical care for allergic contact dermatitis from PI and/or PO. An estimated 29 million have had one or more severe reactions. Those in this group who have successfully managed their allergy by avoidance will not be early adopters, but may want to resume activities with a significant exposure risk once the benefits of groups of our treatment are proven in large numbers of users. Informal surveys, asking adults if they'd want a way to turn off these allergies that's

safe, effective, convenient and affordable, elicit often surprisingly enthusiastic YES responses, in 3-5%, which translates to 11 to 18 million potential users. These are individuals for whom avoidance is either impossible or impractical, for whom impact on quality of life is severe even if reaction intensity is not. Tis entire population are potential users. Many will also be early adopters, because unlike the one-time severe reactor who may want to go back to camping or gardening, they're having symptoms NOW and they want relief NOW.

Other immunotherapy antigens were marketed for PI and PO until 1994, when amendments to the Food Drug and Cosmetic act first required proof of efficacy as well as safety for allergenic products derived from natural source materials. It was my experience and also that of other allergists that those products provided significant partial relief for many severely allergic patients but no manufacturer of a previously licensed product submitted efficacy data. While they provided significant partial relief for many severe patients, however, none of those products achieved ADBP and none yielded the response statistics of our ADBP immunotherapy antigen.

Authors of review articles in 2016 (6) and again in 2019 (7) and 2024 (8) stressed the need for a more effective way to induce tolerance to these antigens. ***We submit that our technology satisfies this need.***

THE APPLIED SCIENCE OF OUR STRATEGY OF COST-EFFECTIVE COMMERCIAL SCALE PRODUCTION

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, called congeners, 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. Suggestions in the medical literature that different congeners differ in their antigenicity are consistent with the general principle that among otherwise structurally similar compounds, those with greater numbers of closely spaced unsaturated bonds will be more allergenic because of their greater structural rigidity. For these reasons 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 chose to solve the need for end-product lot-to-lot consistency by building the necessary consistency into the crop from which our immunotherapy antigen will be made. The owner of the field that has been our source of leaves since 2008 has never seen any berries, suggesting that it's composed exclusively of male plants. Its vigorous growth and proliferation without fertilization by pollination can only come from asexual reproduction. This tells us that our field is probably populated by a relatively limited number of genetic strain of plants that are vigorous in their growth and proliferation as well as in their therapeutic efficacy. In pilot runs hydroponic vegetable farmer and team member Merlin Weaver achieved a cloning efficiency of ~75% with nodes (leaf + stem + adjacent segment of vine) with vines from the same field. He also confirmed that with maintenance of greenhouse temperature and 16 hours per day of supplemental LED lighting he could prevent seasonal dormancy and keep plants growing and producing leaves for 12 months of the year. As soon as our assay is funded and operational we'll be able to identify and clone nodes from long and healthy vines with homogeneous genetically determined urushiol congener distribution patterns. This will let us populate our cultivation greenhouse with plants pre-selected for sufficient consistency in the genetically determined congener distribution patterns of their leaves and stems to automatically build the lot-to-lot and year-to-year consistency required by the FDA into the crop from which we prepare our immunotherapy antigen.

We will remove the 2/3 by wt natural water content of fresh leaves by drying in a vented circulating microbiological incubator at 50 deg C, as water present during vacuum concentration can cause unintended precipitation and even trace water content can facilitate biodegradation of urushiol (9). Urushiol will be extracted from dried leaves with ethanol and the resulting crude ethanol extract vacuum-concentrated to a urushiol content slightly greater than the 100 mg / ml at which strength it will be used for treatment. Concentrated crude ethanol extract of dried leaves is not only much less expensive to produce than purified urushiol at the same concentration; it is also more effective. The latter finding tells us that the crude ethanol extract contains an unidentified substance that contributes to effectiveness but is lost in the process of purification. This is not a regulatory problem for allergenic products derived from natural source materials. Unidentified substances are present in all or nearly all FDA-approved allergenic products derived from natural source materials, and are not a regulatory problem as long as production methods are standardized to make the lot-to-lot content of unidentified ingredients as reproducible as is practically possible.

Lots of urushiol concentrate will be diluted to precisely 100 mg / ml and shipped to team member Millan Bhatt's Molecular Pharma Group FDA 503b compounding pharmacy in New Providence, NJ, where they will be filter-sterilized (as ethanol does not satisfy the FDA's requirements for terminal sterilization), and aseptically packaged in multi-dose injection vials under desiccating conditions.

Both our cultivation and production strategies are sequences of tested and proven technologies. There is nothing new to be developed that might fail.

SAFE & EFFECTIVE ALLERGY SHOTS WITH AN FDA-APPROVED PATHWAY TO BIOLOGICS LICENSURE

We followed our first successful induction of tolerance by offering the same treatment to others. 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 to initial treatment with our most effective formulations and doses and a 100% response in those patients with an unsatisfactory or sub-optimal initial response who accepted our offer of a booster dose.

Response to the low cumulative treatment doses given to our first four patients was strongly correlated pre-treatment (Tx) patch test sensitivity but we observed no such correlation with the 20-fold higher doses we subsequently found to be 90-100 effective. We also found no correlation between pre-Tx patch test sensitivity and reported clinical severity. 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 (10). This contrasted with a no-greater-than 2-fold variation in patch test response in either absence of Tx or lack of clinical response. This finding forms the basis of the FDA's willingness to let us both validate our assay and eliminate the need for separate placebo arms of our clinical trials by testing each study subject twice before treatment (to both confirm that between-test variation in the absence of treatment does not overlap with our proposed endpoint of a 10-fold or greater response and allow the difference between each subject's two pre-treatment tests to be his/her own placebo control, and to accept our a 10-fold or greater reduction in patch test sensitivity as the primary endpoint of both our Phase 1 dose ranging and Phase 2 pivotal clinical trials.

I want to call to the attention of potential investors the extent to which the FDA's agreement to accept our proposed 10-fold reduction in patch test sensitivity as the primary endpoint both Phase 1 dose-ranging and Phase 2 pivotal clinical trials, reduces our risk of regulatory failure. It gives total protection from the unfortunately not uncommon risk inherent in placebo-controlled clinical trials, that the placebo group will

happen to do well enough that the treatment effect isn't doesn't achieve statistical significance. It further gives us a pivotal clinical trial design that essentially replicates each of the immunotherapy antigen, the subjects and the dosing schedule and the primary endpoint with which we previously achieved 90-100% efficacy with no significant adverse events.

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 where 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 compare the shelf-life stability of cost-saving options for product storage and shipping, validate the production strategy we designed for precise, cost-effective commercial scale manufacture, and make clinical trial treatment antigen.

PRE-CLINICAL R&D

Highly purified urushiol was less effective as an immunotherapy antigen than when it was mixed with a small amount of crude, unpurified extract. This told 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 formulations 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 immunotherapy antigen will thus join the large majority of FDA-approved allergenic products made from natural source materials, for which the agency requires either direct or indirect assays of known active pharmaceutical ingredients but addresses the task of standardizing the content and activity of ingredients that cannot be identified, with standardization of preparation protocols.

Round 1 funding will allow Prof. Yang to set up her low-cost urushiol assay, for which we are preparing an application 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 scale of $50-75 per assay while the cost of the quantitative molecular assay is ~$800. Our use of her semi-quantitative assay when an exact molecular assay is available is also not a regulatory problem. Many FDA-regulated allergenic products derived from natural source materials are standardized by other-than-quantitative molecular assays even when such assays exist and are potentially available.

When our Round 1 is funded and her assay becomes available we will begin shelf life stability studies for antigen made from naturally growing PI under different conditions of storage. We will compare storage at room temperature with storage under refrigeration. If the major congeners of the strains we choose to clone and cultivate as our antigen source are stable at room temperature, that data will let us ask the FDA to permit room temperature storage, reducing our cost to provide antigen for 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 refrigeration. If there is no adverse effect of 14 days at 40 deg C we can ask the FDA to let us 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 track longer term thermally stressed shelf life stability at both 50 and 65 deg C, at which stability will support requests to extend authorized use life at lower storage temperatures beyond what time will have let us actually measure at those temperatures. Published data suggests that the most critical factor for long term urushiol stability is protection from even trace contamination with water (8). We plan to employ handling methods that minimize risks of water-contamination at all steps of processing.

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

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

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 preselected to be identical or nearly identical. While ethanol is functionally self-sterilizing it does not by itself meet GMP requirements for terminal sterilization. The antigen and any ethanol needed for dilution within the clean room will be passed into Milan's clean room through sterilizing filters before final assay and GMP-compliant packaging.

In the only published characterization of urushiol extracts of dried leaves Spain and Cooke (8) used an extraction ratio of 9 ml anhydrous ethanol per gram of dried leaves. Our own small observational trial suggests that it may be more efficient for us to use a lower extraction ratio. This will reduce costs to both purchase new ethanol and dispose of used ethanol as a flammable hazardous waste. It will also reduce the time needed for vacuum concentration.

FDA practice, at least in its evaluation of allergenic products derived from natural source materials, is to encourage applicants to schedule pre-IND meetings to review their data, address questions, and make "recommendations" that it will then approve if the applicant then submits a formal IND (Investigational New Drug) application that follows those recommendations. We'd requested our pre-IND meeting long before having a clinical trial antigen with the properties we'd need to know to prepare for clinical trials, to address a different set of questions, though we'd stated our complete development plan including clinical trials in the application. The two allergists on the FDA team that will regulate our product volunteered being enthusiastic about the prospect of being able to approve a safe and effective treatment for these allergies and deviated from our submitted list of questions to tell us, hey, on our own we've looked at your stated clinical trial design and we'd like discuss our thoughts, after which they gave us their "recommendations."

OUR ASSESSMENT OF THE HISTORY BEHIND THE FDA'S ENTHUSIASM FOR THIS PRODUCT

Relevant history, to the best of my knowledge, is that the previously licensed product was good but not as good as our ADBP formulation. The senior allergist member of our FDA review team was the one who in 1991 gave the previous product's manufacture a 3 year notice to provide efficacy data, his intent being that they'd collect the data to tighten up their dosing recommendations which had previously said only that it could be given either by injection or by mouth and with no specific dosing information. The manufacturer's PhD-level scientist in charge of the product wanted to do that, but company management decided instead to study oral dosing which they hoped to sell without need for a prescription. I can tell you from personal experience that treatment by both routes could help severely allergic patients, though oral dosing was significantly less effective than injection. For comparison, neither achieved the complete tolerance of our product.

The previous manufacturer did not have what we have, a quantitative patch test that correlates so strongly with an obvious clinical response that the FDA was willing to accept it as a primary clinical trial endpoint. This left them subject to the hazards of any placebo-controlled clinical trial for which the outcome is a clinical response to a random natural exposure. To achieve objectivity, the pass/fail criteria of the primary endpoint of a clinical trial must be defined BEFORE the trial begins. The smaller the

difference you want to detect as your measure of efficacy, the larger the numbers of subjects you have to study, increasing costs. If natural variation in exposure gives your placebo group a good enough outcome in the absence of the treatment you want to validate, no matter how much your treatment actually helped its recipients, you may fail to achieve your pre-set target for a statistically significant superiority of treatment compared to placebo. This was what happened, and the manufacturer chose not to re-invest in another large and costly study.

My impression is that the FDA team and particularly the allergist who'd pushed the button to demand compliance with the new requirement felt betrayed. They'd initiated their action to motivate the manufacture to produce efficacy-related dosing data for a product generally recognized to be beneficial, when administered by subcutaneous injection. Instead, the manufacturer gambled and lost in an effort to register oral dosing which was known to be less effective but would have been more profitable if approved for over-the-counter sale.

CLINICAL TRIALS:

Following are our current plans to implement the no-obstacles pathway the FDA gave us in our original pre-IND meeting. We will bring them to the table for a second pre-IND meeting when we have optimized cost-effective manufacturing, storage and shipping protocols and when we have congener distribution data for the formulation we want to bring to clinical trial. The most economically significant features of this pathway for investors are:

1) The FDA's acceptance of our simple and objective clinical trial endpoint (a 10-fold or greater fall in sensitivity as measured by our quantitative patch test) instead of having to demonstrate clinical superiority to a placebo control group in response to natural exposures that can have a high degree of natural variability,

2) The procedure proposed to us by one of the FDA allergists on the team that will regulate our product, by which we will both validate our assay and avoid the need for any placebo control arms by testing each subject for urushiol sensitivity twice before and once again after treatment.

3) The FDA's acceptance of a pivotal clinical trial protocol that essentially replicates every parameter of what we've already demonstrated to be 90-100% effective with no significant adverse effects in our human proof-of-concept experience, and

4) The FDA's 100+ years of regulatory experience with both ingredients of our product as a result of which they see no need for the large and costly Phase 3 needed to look for rare side effects of any new product not previously studied in humans.

Choosing clinical trial treatment schedules for maximum marketability: The efficacy of our immunotherapy antigen 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 relative dosage increments between steps of 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 similar settings without on-site 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.

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 immunotherapy antigens from the market in 1994 when their sponsors failed to submit data confirming efficacy. He and his team were enthusiastic about the prospect of being able to license safe and effective shots for these allergies and offered us an obstacle-free pathway through the regulatory process. They proposed that we patch test every study subject twice before treatment and a third time after treatment, so that the difference if any between each subject's two pre-treatment patch tests would constitute his or her own placebo control. They recognized our finding of a 100% correlation between a 10-fold or greater loss of patch test sensitivity following treatment and the achievement of clinically relevant immunological tolerance, by agreeing to accept a 10-fold or greater reduction in patch test sensitivity as our primary clinical trial endpoint with 12 month quarterly questionnaires to track maintenance of tolerance as a secondary endpoint. They further agreed to a pivotal clinical trial design that essentially replicates both the treatment antigen and the recipient population with which we achieved 90-100% efficacy with 100% safety in our human proof-of-concept experience.

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 this 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 booster doses without adverse reactions. We did not encounter any loss of tolerance in less than 13 months in human proof-of-concept responders to the doses we want to bring to clinical trial, though some patients lost tolerance by 2 years. We will incentivize clinical trial subjects to return for repeat patch testing 12 months after completion of initial treatment with an offer of a free booster dose in addition to an honorarium

Achieving and maintaining FDA approval for administration in retail pharmacies will depend on not having significant numbers of reactions that either a physician or a reasonable patient might perceive as needing medical care. We will ask the FDA to authorize clinical trials of booster safety and efficacy given 12-13 months after completion of initial treatment, to validate booster dosing 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.

We plan to offer a post-marketing dose-tracking database to make it easy for patients to get accurate sequential doses at any participating retail pharmacy in the U. S. (This will not apply to clinical trial subjects who except under very unusual circumstances must complete their clinical trials at their originally registered centers.) For any patients (not clinical trial subjects) who have not completed the FDA-approved initial treatment schedule within a consecutive 4-month period, we'll request permission from the FDA to write corrective measures short of requiring repetition of the entire treatment schedule into the program based on general principles of allergen immunotherapy, without having to specifically having to validate each individual deviation by clinical trial. The database can be configured to notify patients at 10, 11 and 12 months that it's time to get boosters. Because of inability to determine which patients who miss their 13-month booster dosing interval will need what dose adjustment to prevent injection site reactions that could require treatment without repetition of patch testing, the dose-tracking database will prescribe repetition of the complete initial treatment series for all patients who miss their 13-month booster target. We see rigorous booster schedule enforcement as essential to maintain a sufficiently benign adverse reaction frequency-severity profile for the FDA to continue to allow retail pharmacy administration.

Organization and conduct of clinical trials: Our business model, whenever practical, is to avoid the need to reinvent the wheel by finding subcontractors who have both the expertise and the resources to efficiently perform various elements of our project. When other factors are equal we try to prioritize subcontractors for whom we are as important a part of their business as they are of ours, to create mutual incentives to collaborate in ways that maximize each party's value to the other. We are currently in discussion with one private allergist-owned and one university-based allergy clinical trial center as potential subcontractors to serve as clinical trial principal investigator and manage our clinical trials in a manner similar to that by which hydroponic vegetable farmer and team member Merlin Weaver's staff will manage our cultivation greenhouse on his farm, chemist and team member Cathy Yang will perform urushiol assays at her institution or a related facility in California, and FDA 503(b) compounding pharmacy director and team member Millan Bhatt will coordinate GMP aseptic packaging. Other options include a VC company that has its own clinical research organization. As a back-up option, should it become necessary, I personally have the contacts to recruit and coordinate individual clinical trial centers managed by allergists who serve with me on the Immunotherapy Committee of the American Academy of Allergy Asthma and Immunology. Team consultant member Scott Oneto independently works with large employers in the western states with workforces occupationally exposed to PO and advised us that if needed and if approved by both the FDA and the IRB, one or a consortium of these entities might want to not only host but possibly also contribute to the funding of a clinical trial to allow early access to treatment to their occupationally exposed allergic employees.

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 on a 1-10+ severity scale setting their personal pre-treatment severity as their personal 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 antigen to be commercially available).

Trials of annual booster safety and efficacy: Depending on subject numbers to be negotiated with 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. Our 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 a significant frequency of 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 approved use life: Initial clinical trials will of necessity be performed with relatively new lots of antigen. Urushiol is not its only active ingredient, making it necessary to document any request to extend shelf life with clinical trials as well as urushiol assays.

We confirmed that an unidentified substance present in crude ethanol extracts contributes to the efficacy of the antigen 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 formulation. We don't know what this substance is, which is not a problem under FDA regulations for allergenic products derived from natural source materials. With no other way to measure its own shelf life stability our only way to validate extensions of use life for the product that uses it 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 antigen.

Extending labeled use life will help rather than hurt sales: Use life stability testing beyond two years is seen as an economic liability in much of the biopharmaceutical industry: Two years will almost always get a product through the supply chain with at least a year of remaining use life when it reaches the buyer, who, if he absolutely needs to have it, will buy more when remaining stock on hand goes out of date. We not only differ philosophically in wanting to be paid well for a product that is also cost-effective for the buyer, but we also believe that a longer use life will also help sell more product. Our major buyers will be retail pharmacy chains and pharmacies, many in locations in which anticipated demand will be light. The longer the use life we can provide for both unopened and opened multi-dose vials, the larger the number of locations at which potential buyers will calculate that demand for shots will cover their cost of stocking the antigen in potentially low demand locations. Large volume buyers may want to negotiate up to specified % of refund options for stock that has gone out of date without being used. The longer the use dates for which we can get FDA approval, the less of an issue this will be and the more willing buyers will be to stock the product in potentially low demand locations.

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

The urushiols of PI and PO are sufficiently cross-reactive that allergy shots that work for PI are just as likely to work for PO. Until it's confirmed in clinical trials, however, it cannot be guaranteed. In the unlikely event that our antigen meets efficacy criteria for PI rot not for PO our plan would be to license it for PI alone, which is the predominant 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 antigen from PO to be cultivated under similar conditions. We could then make and validate a combination product containing concentrated ethanol extracts of both plants. If we are able to confirm both safety and efficacy for our initial single plant source antigen for allergy to both PI and PO, however, it will be much more economical to make a single product from a single cultivar of plants that we already know grow well both outdoors and in greenhouses in our location, than to have to maintain cultivars of two separate plants and separately process two sets of leaves to make and combine two separately manufactured ethanol extract concentrates into a final product.

Post-marketing surveillance:

We can use the same dose-tracking database to invite patient to report both duration and any loss of clinical tolerance and any suboptimal experiences they may encounter in association with treatment. This data will give us guidance toward product improvement over time.

ADBP BEYOND PI & PO:

The innovation that gives ADBP its potency is its exploitation of micropinocytosis (1), the phenomenon by which naïve antigen-presenting cells (APCs) gobble up particles in the 0.5 to 5 micron size range. To the best of our knowledge ADBP is unique among drug delivery technologies in its ability to instantly populate a volume of a non-liquid target tissue with hundreds of thousands to millions of clumps of an antigen-of-interest in bite-sized snacks for naïve APCs. Our outcomes with PI suggest that these clump-fed Aps deliver a much stronger signal to the immune response switching mechanism than may otherwise be achievable, and that similar force-feeding of APCs may deliver a similar boost in signal strength for other therapeutic applications of immunomodulation.

The cellular mechanisms of immunomodulation are the same in different directions. Methods to bias switching between different directions are beyond the scope of this discussion. We see promising and technologically feasible applications to immunomodulation from naiveté to protective sensitization against infectious diseases. An example for which we've already designed step-by-step protocol that can be validated at every step (before having to invest in the next step) is a COVID-19 vaccine that in comparison to mRNA vaccines is safer (without the numerous immune system complications), more effective (preventing infection instead of reducing symptoms and creating asymptomatic spreaders), less subject to loss of efficacy with mutations in the virus (by using conserved immunogenic epitopes as antigens) and without the mRNA vaccine requirement for ultra-cold storage. Other promising and also technologically feasible applications involve immunomodulation from tolerance to protective sensitization against epitopes of the tumor-specific antigens on the surface of every cell of every cancer. For all of these applications the antigens are immunogenic peptides. The challenge to use ADBP for peptide antigens is to make versions with the solubility properties required for ADBP without loss of antigenicity. Our solution to this problem is to make solubility-modified versions of the peptide epitopes of interest with solubility-modifying nonsense protein end-chains by solid phase synthesis, for which our patent application is pending.

The antigen-presenting receptor to which urushiol binds in the APC has been identified as CD1a, a member of the class of CD1 receptors that present lipid antigens in the same manner that MHC receptors present antigenic peptides (13). The verifiable initial steps of our proposed protocol for the development of a better COVID vaccine can confirm whether ADBP force-feeding of APCs with 0.5 to 5 micron clumps of peptide antigens achieves a similar booster of MHC receptor saturation and enhancement of immunomodulation to that achieved by urushiol force-feeding and enhancement of CD1a binding. If this effort is successful, the sky is the limit for peptide epitope antigen applications of ADBP. Other peptide epitope applications to immunomodulation from sensitization to tolerance include anaphylactic food allergies and non-anaphylactic food allergies such as eosinophilic esophagitis and the full spectrum of autoimmune diseases

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

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