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### **WHAT IS PHYTOLOGIX®**

- PhytoLogix® is a technology platform for identifying and studying the unique bioactive natural products and then developing them into proprietary standardized extracts for use as novel ingredients in cosmeceutical, nutraceutical, pharmaceutical products.
- PhytoLogix® comprises three fundamental building blocks: 1. Natural product library; 2. Dereplication and informatic database; 3. Bioassay guided discovery screen.

### **WHAT IS PHYTOLOGIX® PLANT COLLECTION LIBRARY**

PhytoLogix® natural product library possesses a collection of more than 11,000 documented medicinal plants and more than 600 marines from 24 countries. Those collections represent 440 plant families, 2940 plant genus and 5207 unique plant species with 1-2 kg of wild collected biomass plus voucher taxonomy for botanical identification. Those medicinal plants not only have documented human consumption history for medicinal purpose, but also >25% of the collection are utilized in source countries as food ingredients or >20% plants are listed in USA as DSHEA Grandfather Plants.

### **WHAT IS PHYTOLOGIX® EXTRACT AND FRACTION LIBRARY**

Unigen is utilizing an accelerated, automatic extraction technology to produce two extracts – organic and aqueous extracts from each plant. PhytoLogix® natural product library contains more than 15,000 plant extracts stored in 96-well plates and ready for high throughput discovery screening. Unigen has also developed a proprietary methodology to fractionate plant extracts with high throughput purification (HTP) system. Every plant extract can be fractionated into 88 fractions to be stored in a 96-well plate for discovery screening and dereplication. PhytoLogix® natural product library has a possession of >300,000 HTP fractions with close to 1,000 pure compounds.

### **WHAT IS PHYTOLOGIX® DATABASE**

A proprietary informatic database that links the indigenous wisdom with modern scientific research has been established. It includes a relational database that integrates data from field collection, botanical identification, traditional application, geological distribution, and growth condition with DNA bar coding, biological screening, chemical structure dereplication, and compound isolation and identification.

### **WHAT IS “DEREPLICATION”**

“Dereplication” refers to a process of analyzing, without isolation, a fraction or an extract for physical, spectroscopic and structural information; comparing the information with internal and commercial databases; reaching to a conclusion on the existence of novel and/or known compounds; and determining the strategy of further investigations. The efficiency and the quality of the dereplication program will determine the lead-time from obtaining the primary screen results to the discovery of novel chemical entities. The dereplication technology developed at Unigen focuses on improving the efficiency and accuracy of the dereplication process by integrating the bioactivity profile with LC/PDA/MS & NMR profiles from hit HTP fractions.

### **WHAT ARE “HTS” AND “HTP”**

“HTS” is refer to “High Throughput Screen”; and “HTP” is refer to “High Throughput purification”. Accelerated bioassay guided random screening and discovery initiated with marketing driven selection of therapeutic indication and biological targets. High throughput screening models based on proteins, genes, cells and other state of art discovery platforms such as HTS chips have been applied to the extracts and fractions from PhytoLogix® natural product library. HTP is a high speed fractionation process using parallel and preparative column chromatography to generate 96 fractions from each plant

extract. The active isolation and identification process follows a scaled-up HTP fractionation protocol and the guides from structure dereplication and bioassay. Once the active HTP fractions are identified for lead compound isolation, it usually takes few weeks to complete large-scale re-extraction, active isolation and identification.

### **HOW MANY TIMES THE PHYTOLOGIX® LIBRARY HAS BEEN SCREENED AGAINST BIOLOGICAL TARGETS**

Since the establishment of PhytoLogix® platform in 1999, Unigen has carried on 23 discovery projects targeting many health issues facing the world population, such as osteoarthritis, diabetes, obesity, hepatitis, chronic pain, cognition function, immune function, solid tumor, atypical dermatitis, microbial infection, skin wrinkle and uneven skin tone. Six discovery projects commercialized novel ingredients such as Univestin (joint care), Nivitol (even skin tone), Uniflavin (skin irritation), Loesyn (insulin sensitizer), Pematrim (weight management), and UP1307 (body care). Two discovery projects have lead compositions – UP480P (natural preservative) and UP274M (even skin tone) under human safety and efficacy evaluation; three projects under different stage of investigation.

### **HOW DO YOU MANAGE PHYTOLOGIX® DISCOVERY PROCESS**

Unigen is utilizing a stage gate system to manage PhytoLogix® discovery process. As showing in the following scheme, from commercial strategy to product launch, the discovery process includes a total of 6 stage gates. Each stage, there are multiple well defined deliverables to measure the milestone achievements and to facilitate the decision making process for moving forward into next stage of development. Those milestones and stage gates can also be utilized to evaluate the productivity and viability of the discovery and development process that can be linked with milestone payments.

### **ANY EXAMPLE FOR DRUG DISCOVERY USING PHYTOLOGIX®**

More than 15 years of research collaboration with NCI and Josephine Ford Cancer center in discovery of anti-solid tumor drug leads using PhytoLogix® platform has completed the screening of 21,246 plant extracts, 22,088 HTP fractions, and 1372 enriched fractions and 114 pure compounds. Pursuing positive hits has yielded 58 compounds reduced solid tumor growth in vitro from which 5 pure compounds with potent solid tumor selectivity have been moved into pre-clinical drug development in 2016 under a 3-party collaboration with Ford Cancer Center and Peking University.

### **ANY COMMERCIALIZATION SUCCESS OF PHYTOLOGIX®**

Unigen is utilizing PhytoLogix® platform to identify unique bioactive natural products and then to develop them into proprietary ingredients in cosmeceutical, nutraceutical and pharmaceutical products. Back to 1999, the first year of the establishment of PhytoLogix® platform, 1230 medicinal plants from Unigen's PhytoLogix® library were screened to identify natural substances with COX and LO dual inhibitory activity. Following confirmatory assays with freshly prepared materials and dose response titrations, the best of the "hits" from the screen were selected for assay-guided HPLC fractionations to isolate and identify pure active compounds. The first discovery project yielded a proprietary ingredient - Univestin that has been manufactured and sold worldwide in 8 countries including USA, Canada, Australia, Japan, S. Korea and UK. With 52 issued global patents and 23 peer-reviewed publications, Univestin became one of the key ingredients in global joint care brands formulated in 36 dietary or functional food products by 28 companies with more than 6+ Billion doses of Univestin were consumed in past 15 years.

The second project using PhytoLogix® platform was screening more than 2000 plants for tyrosinase inhibition. This discovery project produced 64 active extracts and detected 6 different types of active natural entities with one compound - UP302 (Nivitol) identified as one the most potent tyrosinase inhibitors even known in 2003. It took another 6 years to completed total synthesis of this minor component in Flex Lilly and licensed under exclusivity to Estee Lauder and commercialized in 15 global even skin tone brands.

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