***Value of the SBIR/STTR Project, Expected Outcomes, and Impact***

***Summary***: Our program explores the therapeutic potential of a genetically-optimized lectin as a broad-spectrum antiviral agent with an initial target indication of treating severe influenza. The lead lectin derivative, termed H84T due to a threonine at position 84 in lieu of histidine, shows high potency against important respiratory viral pathogens like the influenza virus, including pandemic and resistant strains. H84T works by binding to surface mannose structures of enveloped viruses and blocking their entry into host cells. Prior work has shown that lectins are mitogenic and can stimulate viral replication, leading to unwanted inflammatory pathology. However, by mutating a single amino acid we minimize this toxic effect, yet maintain very potent antiviral activity. This leads us to consider H84T a promising broad-spectrum antiviral candidate. We propose to further test H84T against multiple strains of seasonal and pandemic influenza *in vitro* and *in vivo*. *We will conduct the necessary research to advance H84T through preclinical development and open an Investigational New Drug (IND) application. This promising anti-influenza therapeutic will ultimately be licensed to a clinical-stage pharmaceutical partner, who will commence with commercialization on a global scale.*

***The Problem:*** Influenza (“the flu”) is an infectious disease caused by RNA viruses that affects birds and mammals. Human influenza A and B viruses cause two seasonal epidemics per year—one per hemisphere—resulting in three to five million severe cases and around 500,000 deaths globally [1]. Although the incidence of influenza can vary widely by season, approximately 36,000 deaths and more than 200,000 hospitalizations are directly associated with influenza every year in the United States [2]. Current options to prevent and treat the flu include vaccines and antiviral drugs, respectively, and each has its limitations. First, vaccines are only effective against certain strains of the virus with seasonal efficacy ranging between 10% and 60% [3] [4]. Second, vaccines can only be used prophylactically and large portions of the population opt not to get vaccinated. Third, there are cost and accessibility/availability issues, as stocks expire at the end of each season and need to be replenished. A combination of these factors result in poor vaccination coverage, typically less than 50% of the overall population for any given year and even less (<20%) during pandemics (more information in “Market” section).

Next, there are two major classes of influenza antivirals: adamantanes (amantadine and rimantadine) and inhibitors of influenza neuraminidase (oseltamivir and zanamivir). Similar to vaccines, resistance among “pandemic” virus strains and poor efficacy affect both classes of drugs. In fact, the Centers for Disease Control and Prevention (CDC) no longer recommends adamantanes “for use in the United States at this time because of high levels of antiviral resistance to these drugs among circulating influenza viruses” [5]. Examples of resistance to neuraminidase inhibitors (NIs) include influenza A (H1N1) with an H275Y mutation, which is resistant to oseltamivir (Tamiflu®) and responsible for the 2009 swine flu pandemic, and oseltamivir-resistant A(H1N1)pdm09 infections, predominant in the 2013-2014 flu season. Both strains have a mutation on their neuraminidase gene, conferring resistance to this entire class of flu antivirals.

***The Solution:*** We believe H84T has commercial application as a novel anti-influenza treatment and broad-spectrum antiviral drug characterized by its ability to bind a wide range of different glycoproteins containing mannose-rich structures. These properties have shown to inhibit viral replication in resistant strains of influenza *in vitro* and have implications for the treatment of wide variety of economically- and socially-important respiratory diseases caused by viral pathogens. As stated above, our first indication will be the treatment of severe influenza A and B in hospitalized patients. We believe this patient group will benefit the most, as these patients are not responding to conventional antiviral treatments that may have developed resistance. Additional indications include: MERS and SARS corona virus, HIV, hepatitis C virus (HCV), and Ebola (EBOV). All of these viruses are enveloped viruses containing mannose structures and are viable therapeutic targets for H84T.

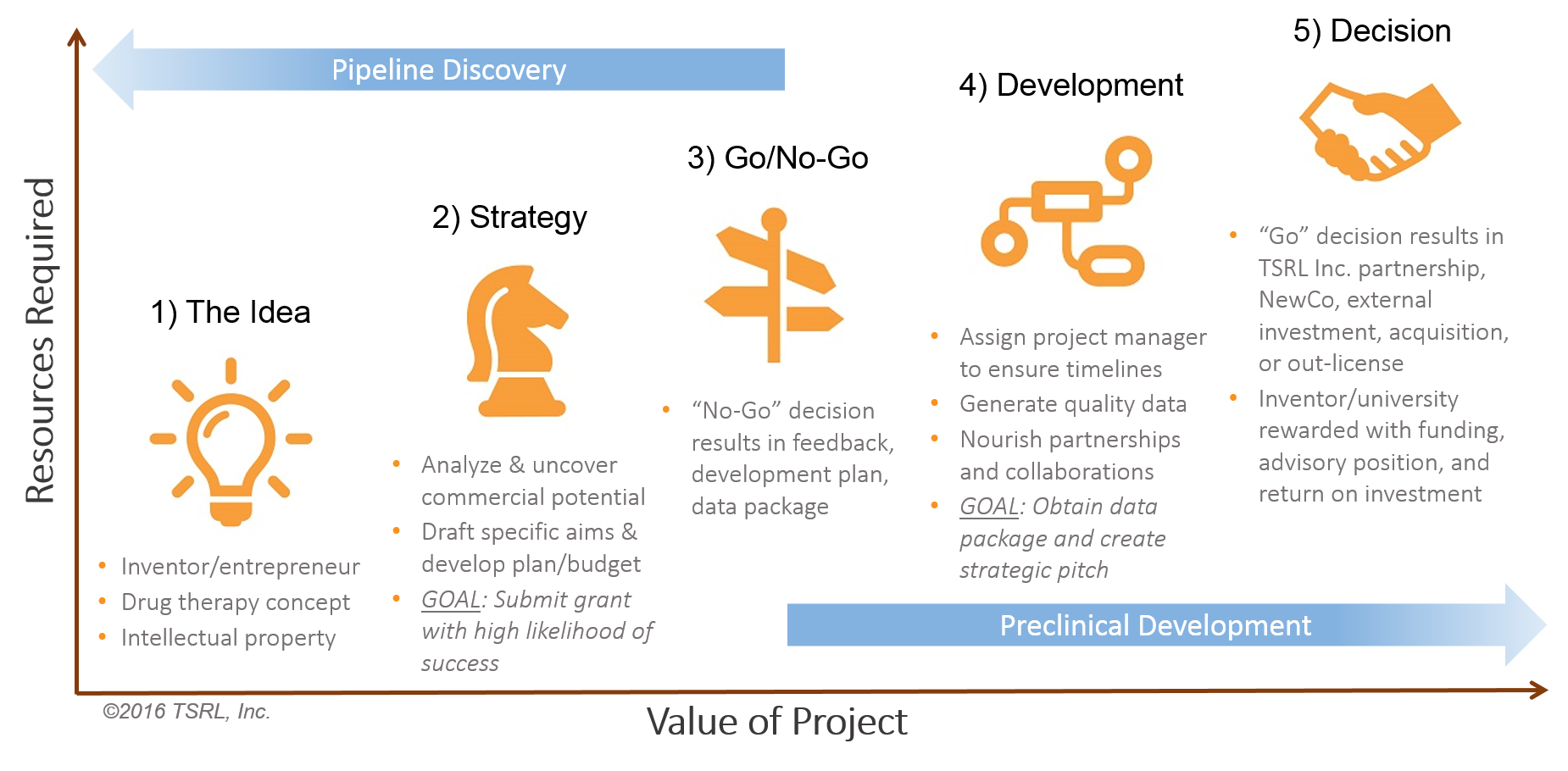
Potential societal, educational, and scientific benefits to this work tie together epidemiology, immunodeficiency, and critical care medicine. An ongoing debate weighs the consequences of prescribing NIs to non-hospitalized patients [6]. On one hand, the Food and Drug Administration (FDA) contends that NIs do not have a positive impact on population health, citing lack of symptom and hospitalization reduction. They express concern that healthy people with flu-like symptoms flood emergency rooms to receive the antivirals, potentially spreading disease to the sick and elderly, who are more susceptible. On the other hand, the CDC cites evidence that NIs shorten duration of sickness and reduce length of hospital stay, complications, and secondary bacterial infections [7]. H84T has the potential to overcome resistance concerns stemming from overuse of NIs and addresses the hospitalized patient population that has been exposed to virulent flu.

***The Challenge and the Opportunity***: Pharmaceutical product innovations are risky, resource-intensive, and time-consuming. Only 10% of Phase 1 drugs receive approval after five to eight years of clinical development [8]. Moreover, the average pre-tax cost per new drug approval, including failures and capitalized costs, is estimated to be $2.56 billion [9]. High R&D costs, long timelines, and a strict regulatory environment result in high barriers-to-entry for new drug companies. Despite this, biotech companies are a significant source of new drug discoveries made possible through research collaborations and licensing agreements[10]. Under these partnerships, major pharmaceutical firms (“sponsors”) provide the infrastructure necessary to manufacture and market a new drug developed by smaller companies. This affords the sponsor greater flexibility and agility in their research operations while divesting large portions of the risk until an IND is submitted or clinical proof-of-concept (POC) is achieved. *This SBIR project allows us to generate the data necessary to make a compelling argument for partnership with a sponsor which, in turn, allows our new drug concept to be developed, manufactured and marketed to patients in need of therapy options for influenza and other infectious diseases.*

***Company***

Therapeutic Systems Research Laboratories (TSRL), Inc. is a privately-owned pharmaceutical company based in Ann Arbor, Michigan. We were founded by University of Michigan (U of M) Professor Gordon Amidon, an internationally recognized expert in the field of biopharmaceutics. Our business model initially centered on developing oral drug delivery technologies and orally-administered prodrug approaches for existing drug products. Today, we have begun to establish ourselves as a preclinical accelerator for anti-infective therapeutic concepts. In other words, we provide the infrastructure, laboratory, scientific and business resources necessary to “de-risk” and drive early-stage assets to IND. **Figure 1** illustrates how we add value at each inflection point, with the goal to spin off a new company (“NewCo”) for out-license or acquisition.

**Figure 1**. TSRL Technology Accelerator Value-Add Model



Expansion strategies for TSRL’s technology platforms involve in-licensing drug assets from academic and industry organizations and/or co-developing drug therapy concepts with academic researchers. We design appropriate experiments in collaboration with the inventor(s) and generate data to make an informed go/no-go decision regarding future development. Assuming the project generates IND-enabling data, we spin out the technology into a NewCo, structured as a limited liability company (LLC), and either 1) out-license the asset to a large pharmaceutical partner for clinical development immediately post-IND or 2) continue clinical development to POC (see **Table 1** for successfully out-licensed technologies). In either scenario, TSRL owns an equity stake in the affiliate LLC proportionate to the investment it makes through capital or in-kind services. If our affiliate LLC pursues development organically, we will add individuals with fundraising, clinical development, regulatory, quality assurance, and manufacturing experience.

**Table 1.** Commercialized TSRL Technologies

|  |  |  |
| --- | --- | --- |
| Area | Commercialization Summary | Revenues-to-Date |
| Dosage Form Technology | Licensed technology (# 5,229,131) | $9.2 million |
| Absorption Modeling Software | Licensed software to Simulations Plus | $10.6 million |

TSRL currently employs eight full time employees and generates annual revenues of approximately $2 million from royalties, collaborative research agreements, and grants. A summary of government funding supporting our antiviral therapeutics programs appears in **Table 2**. We conduct our operations in a 7,200 sq. ft. facility with analytical, formulation, cell culture and in vivo testing capabilities. Our scientific team has broad experience in chemistry, molecular biology, biochemistry, analytical chemistry, *in vivo* animal models, PK/ADME, toxicology and formulation. We also have one business development and one finance/administration professional. Management draws on extensive preclinical and clinical drug development experience from academia, biotech and large pharmaceutical organizations.

**Table 2.** Summary of government grants awarded to TSRL in the past five years

|  |  |
| --- | --- |
| Grant # | Title |
| 2R44AI100401-03 | Broad Spectrum Antiviral Nucleoside Phosphonate Analogs |
| 1R43AI112185-01 | Nucleoside Phosphonate Analogs for the Treatment of Adenoviral Infection |
| 1R43AI091216-01 | Novel Prodrugs for Treatment of Human CMV Infection |
| 2R44AI081396-02 | Prodrugs of Neuraminidase Inhibitors for Increased Oral Bioavailability |
| 1R43AI081396-01 | Prodrugs of Neuraminidase Inhibitors for Increased Oral Bioavailability |
| 5U01AI061457 (5 yrs) | Oral Antiviral Prodrugs for Biodefense Initiative |
| 2R44AI056864-03A1 | Improving Absorption and Targeting of Antiviral Drugs |
| 5R43AI056864-02 | Improving Absorption and Targeting of Antiviral Drugs |
| 1R43AI056864-01 | Improving Absorption and Targeting of Antiviral Drugs |

In addition to our core team, we have enlisted academic, medical, and industry consultants with preclinical and clinical influenza research and drug development expertise. Our collaborators from U of M include: David Markovitz, MD, Professor of Infectious Diseases and inventor of the H84T technology, Steven King, PhD, Associate Research Scientist in the Dept. of Internal Medicine, and Bruce Auerbach, Mentor-In-Residence, U of M Venture Center and former COO of AlphaCore Pharma, a biotechnology company acquired by MedImmune. Dr. Markovitz served on the FDA Vaccines and Related Biological Products Advisory Committee as a reviewer on the agency’s annual influenza program. Dr. King offers additional experience in virology and Mr. Auerbach works as a business development advisor.

Furthermore, we have Arnold Monto, MD, Professor of Epidemiology in the Department of Public Health at U of M, as a consultant to the project. Dr. Monto is a key opinion leader in the influenza field. He has served on an advisory board to the National Institute of Allergy and Infectious Diseases (NIAID) and has contributed to the design the annual influenza vaccine. He is also an inaugural director of the U of M Bioterrorism Preparedness Initiative and has been involved with the development of Relenzaand Tamiflu.

For guidance with active pharmaceutical ingredient (API) scale-up and manufacturing, we have recruited two industry experts. First, Anna Schwendeman, PhD, Assistant Professor of Medicinal Chemistry at U of M, has contributed to the discovery and translation of several HDL therapies to Phase II clinical trials at Esperion Therapeutics. She has developed kilo-scale recombinant protein for the largest Phase II sHDL clinical trial to date. In total, Dr. Schwendeman has successfully submitted FDA INDs for six different products including nanoparticles, liposome, proteins, peptides and small molecules. Second, Kent Iverson is an independent CMC consultant with over 25 years of pharmaceutical process development experience. As a member of the fermentation group at Genetech, Mr. Iverson was involved in the approvals of two recombinant protein products: Protropin™ (recombinant metHGH) and Activase (recombinant TPA).

Next, we have committed three infectious disease industry veterans as consultants to the project: John Domagala, PhD, Lori Dostal, PhD, both former directors at Pfizer, and clinical development expert David Horn, MD, formerly with Merck, who will help with developing the target product profile and clinical development plan for H84T. Last, Steve Duddy, PhD is a safety/toxicology expert and former Senior Scientific Advisor within Drug Safety Research and Development at Pfizer. He is currently Partner and Chief Scientific Officer of Integrated Nonclinical Development Solutions, Inc. In addition to those listed, TSRL may bring on more advisors on an as-needed basis.

***Market, Customer, and Competition***

***Market***: The total global market for influenza antivirals—which does not include vaccines—exceeded $1.5 billion USD in 2014, based on worldwide sales of the top two selling drugs Tamiflu® (oseltamivir) and Relenza® (zanamivir). Sales in the United States totaled $800 million in 2014 and grew, on average, more than 25% every year since 2010 (**Figure 2**).

**Figure 2**. Annual US Sales of Relenza® and Tamiflu® [28]

Pandemics, seasonal variations, and government stockpiling efforts all affect annual influenza therapeutics sales and make forecasting difficult. We also make the distinction between addressable markets for antivirals versus vaccines. Although influenza vaccines are recommended as the first line of defense against the flu, they have limited utility during pandemics, mainly because R&D and manufacturing turnaround time to produce effective vaccines in mass quantities result in shortages. For example, only 13% of adults received the flu vaccine in the “swine flu” pandemic of 2009-2010 (**Table 3**). Even during non-pandemic years, flu vaccine coverage averages less than 50% of the population. Due to these factors and the prophylactic use of vaccines, we do not consider them direct competitors in the market analysis, although we recognize they reduce overall market share by preventing more infections. Despite this, we believe demand for effective antivirals will continue to grow and spike during pandemics.

*\*2012-2014 Relenza sales estimated based on royalty revenue to Biota Pharmaceuticals, its developer (Source: EDGAR)*

**Table 3**. Overview of Influenza Outbreaks by Strain

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Influenza Strain | “Pandemic Name”: Year (if any) | Deaths\* | Mortality Rate | Vaccination Rate | Vaccination Efficacy |
| H1N1 | “Swine Flu”: 2009-2010 | 8,870 to 18,300 [11] | 0.01-0.03% | 13% of adults  24% of children [12] | 77% [13] |
| H2N2 | “Asian Flu”: 1957-1958 | 69,800 [14] | 0.01-0.03% | 4% [15] | n/a |
| H3N2 | “Hong Kong Flu”: 1968-1969 | 33,800 | 0.03% | Insignificant | n/a |
| H5N1 | “Bird or Avian Flu” (since 2003) | 263 (worldwide) [16] | 59% | No vaccine | n/a |
| H7N9 | Unnamed (2013) | 46 (China) [17] | 32% | No vaccine | n/a |

*\*Deaths are United States only unless specified otherwise*

***Customer and Segmentation***: We segment addressable antiviral markets by payer and divide into government and commercial customers. Government customers include agencies like the CDC who lead stockpiling efforts during epidemics that occur after vaccine prevention fails or if antiviral-resistant strains emerge. On the other hand, commercial customers include wholesalers and distributors who sell to hospital groups, who in turn administer medication to patients. As a broad spectrum antiviral with an initial indication to treat severe influenza A and B in adults, H84T appeals to both of these markets. However, we expect H84T to have higher utility during pandemics, when up to 70% of total antiviral sales are attributed to stockpiling. Therefore, government agencies and stockpiling efforts are our target customer and initial addressable market, respectively.

To begin, the US government spent more than $1.3 billion (80%/20% Tamiflu/Relenza) over five years to prepare for an influenza pandemic by building up the Strategic National Stockpile (SNS) [18] [19]. At an average cost-per-treatment course of $19.24 for Tamiflu, that covers nearly 76 million doses, or roughly a quarter of the US population. In addition, stockpiles need to be replenished according to the shelf-life of each drug. Vaccines and biologics like H84T have a shorter shelf-life than small molecules, with most flu vaccines expiring in June of that production year and biologics usually having a shelf life of three years [20]. In contrast, lots of Tamiflu and Relenza, which are small molecules, have an expiry of ten years from manufacture [21]. For both products, the FDA has issued an Emergency Use Authorization (EUA) for patients affected by H1N1 influenza, and as a result, is also stockpiling unapproved IV formulations. Similarly, the Biomedical Advanced Research and Development Authority (BARDA) has granted an Australian firm, Biota Pharmaceuticals, a $231 million contract to develop a fourth NI, laninamivir, in the United States [22].

Non-government customers purchase antivirals for commercial stockpiling programs and for treating seasonal flu. For example, there is a Pandemic Readiness for Employers Program (PREP) offered by GSK for Relenza and the employer stockpiling program offered by Roche for Tamiflu. Such programs allow employers to reserve supplies of the antiviral at an annual fee per unit. Supplies are maintained by the manufacturer and delivered only when needed. As a result of these programs, we believe significant sales can be realized from initial and continuous stockpiling of H84T.

Seasonal sales also contribute to ongoing profitability of H84T. The very young (0-4) and the elderly (65+) are the most susceptible age groups to seasonal flu. In the most recent 2014-2015 flu outbreak, 15,249 laboratory-confirmed influenza-associated hospitalizations were reported. **Figure 3** illustrates trends in laboratory-confirmed influenza hospitalizations for the US via cohort and flu season. In general, flu drugs are marketed by a sponsor for short term treatment and as a two month prophylactic regimen, the latter of which accounts for minimal revenues and is not reimbursable in the US. We believe a growing need to replenish stockpiles and treat seasonal flu patients, evident by increasing hospitalizations, ensure a robust market for future novel antivirals like H84T.

Widespread adoption of influenza antiviral drugs is hampered by inaccessibility and inefficacy concerns, as seen with H1N1 and other emergent strains. Healthcare providers reported shortages of Tamiflu during the 2012-2013 and 2014-2015 flu seasons. Limited efficacy, in particular, creates formulary hurdles and reimbursement constraints. Resistance is the leading cause of poor efficacy of approved antivirals. The mainstay therapy, Tamiflu, is seeing increasing levels of resistance, making Relenza and recently-approved Peramivir (Rapivab®) the only treatment options left. To repeat, H84T has advantages over existing treatments by offering a novel therapy option with less vulnerability to resistant virus strains and broad-spectrum activity. *H84T offers a potentially efficacious therapy for treating a variety of severe viral respiratory illnesses at the onset of flu-like symptoms, in addition to laboratory-confirmed influenza A and B.*

*\*Up to week ending March 7th, 2015*

**Figure 3**. Laboratory-Confirmed Influenza Hospitalizations by Cohort and Flu Season [27]

***Barriers to Entry***: Two key barriers to entry in the pharmaceutical sector are 1) high R&D costs and 2) freedom to operate with regards to intellectual property (IP). As previously stated, capitalized drug development costs routinely exceed $2 billion from discovery to approval. To address this barrier, it is common for preclinical development companies to partner with sponsors for clinical development. Our current focus is antiviral therapeutics, which, due to their generally short time of administration, require shorter development timelines and less overall capital to reach the next value-inflection point. TSRL supplements funding awards with internal resources to generate the data required to submit an IND. At this point, out-license, acquisition, or strategic investment are possible options.

IP protection is the second major barrier to entry. Patents that protect composition of matter and therapeutic use as well as pharmaceutical composition and manufacturing processes allow pharmaceutical drug development firms freedom to operate. They build an “intellectual property wall” around their drug candidate that maximizes return on investment (ROI) after product launch. Although patents typically expire 20 years after filing, they are supported by regulatory and country-based regulations like the Hatch-Waxman amendments, which add clinical drug development time to patent life. Data/marketing exclusivity is also granted by the FDA for five years post-approval for new chemical entities (NCEs) that may overlap with existing IP protection. The H84T IP is covered by both composition of matter and method of use and does not expire until the early 2030’s after extensions, well into the commercial lifespan of the final product.

We develop antiviral therapeutics from lead to IND or, if feasible, to clinical proof-of-concept through our accelerator business model. Throughout this process we engage clinical-stage pharmaceutical sponsors in the antiviral space for either strategic investment, out-license or acquisition. **Table 4** lists potential partners with complementary portfolios, global development capabilities and established specialty pharmaceutical sales forces. As stated above, the final drug product is commercialized and marketed by the sponsor. They employ medical science liaisons and qualified sales representatives to educate Key Opinion Leaders (KOLs), prescribing physicians and consumers. Ultimately we want H84T to be included in hospital formularies and reimbursed by the Centers for Medicare and Medicaid (CMS) in in- and out-patient settings. Tamiflu, for instance, is listed as a “Preferred Brand” on many formularies. Likewise, our sponsor works with manufacturers and distributors to offer coupons and other discounts to increase adoption rate. Advertising campaigns target physicians and patients, as evident from Roche’s direct-to-consumer advertisements for Tamiflu.

**Table 4**. Potential Pharmaceutical Sponsors

|  |  |  |
| --- | --- | --- |
| Commercialization Partner | Anti-influenza Therapies | Reason for Collaboration |
| Genentech (subsidiary of Roche) | Oseltamivir (M); MHAA4549A (II) | Patent expires August 2016, PCT expires 2018; room to fill early-stage pipeline |
| Janssen Pharmaceuticals (subsidiary of J&J) | Inflexal V (PM); CR6261 (W); VX787 (II) | Recently in-licensed VX787 from Vertex; possibility to supplement after approval |
| GlaxoSmithKline | Zanamivir (M); Anflu (M); Arepanrix (M); Daronrix (M); Fluarix (M) | No early-stage antivirals in pipeline; H84T can fit as next-generation mist inhalation product |
| Biota/Daiichi-Sankyo | Laninamivir (III) | Partnership for Asian market; H84T can fit as next-generation mist inhalation product |

*(M) = Marketed; (PM) = Post-Marketing Surveillance; (III) = Phase III; (II) = Phase II; Source Medtrack Mar 2015*

***Competition:***  Positioning plays a key factor in marketing and successful adoption. Influenza antiviral drugs directly compete with one another as well as a number of over-the-counter (OTC) products. As stated above, influenza vaccines are not considered for this analysis, as they do not substitute antiviral drugs, but indirectly reduce incidence rates (and market size). Vaccines would only displace antivirals if they succeeded in completely preventing influenza – a scenario we believe is unlikely given annual genetic drift of influenza and the unlikelihood of complete coverage. Our analysis also excludes OTC drugs such as herbal extracts (none of which are clinically shown to be effective against upper respiratory infections) and drugs that are only approved in minor markets (such as naphazoline HCL, an ADRA1 agonist only approved in Hong-Kong). As a result, our analysis is limited to those drugs and drug candidates that have a recent, clearly identified development status in key markets [23].

To begin, there are four globally marketed antiviral influenza products, three of which are approved for use in the US (see **Table 5**). The US market is dominated by Tamiflu® (oseltamivir, Roche) with Relenza® (zanamivir, GSK) holding less than 10% total market share. A third drug, Rapivab™ (Peramivir, BioCryst) was approved in December of 2014. Although all three of these treatments are NIs, they each have different routes of administration. Tamiflu® is given 75mg once per day orally, Relenza® is given as a 10mg twice per day inhalation, and Rapivab™ is administered as a 600mg IV infusion. The latter is used to treat critically ill patients, particularly from pandemic “swine flu” and, given the reports of increasing resistance to Tamiflu® starting in the 2007/8 flu season, is now considered a major competitor.

**Table 5**. Currently Marketed Influenza Therapeutics

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Agent | *Sponsor* | *ROA* | *Pros* | *Cons* |
| Relenza | GlaxoSmithKline | Inhalation | Delivery to the site of virus entry (lung) | Bronchospasm side effects; Inhaler needs practice; impractical for ill patients |
| Tamiflu | Roche | Oral | Ease of administration and distribution | Emerging resistance (i.e. H1N1); supply shortages |
| Inavir | Daiichi-Sankyo (Japan only) | Inhalation | Single dose administration;  Prevention and therapy | Brochospasm side effects; inhaler needs practice; Impractical for ill patients |
| Rapivab | BioCryst | Infusion | For severe and complicated cases; No current resistances | Physician administration; limited accessibility |

As of December 2015, there were 72 non-vaccine antiviral products in active preclinical and clinical development with influenza as a potential therapeutic indication. They represent about a third of total anti-influenza product programs (**Figure 4a** and **4b**) [23]. Furthermore, there are several novel and re-formulated therapies in advanced clinical development (see **Table 6** for select therapies). Late-stage clinical approaches trend toward formulations with higher systemic exposure to stop the spread of virus earlier and/or less invasive routes of administration (ROA) to improve patient compliance. Therapeutic approaches in pre-clinical and early clinical development have various formulations, targets and mechanisms. For instance, inhalation mists are a common ROA for large molecules like biologics. Molecule classes such as monoclonal antibodies (IV), hemagglutin inhibitors, and immunostimulants are also found throughout the pipeline. Last, there are two investigational therapies with interferon as the target, administered by IV. *We believe our goal of developing H84T for IV administration ROA is consistent with the ongoing trends addressing virus dissemination in severely ill patient populations.*

**4b**. Active Antiviral vs Vaccine Programs

**Figure 4a**. Total Active Antiviral Programs in Development

Next, we have included recombinant human mannose-binding lectin (rhMBL) in **Table 6**. Despite a similar mechanism of action as H84T, this compound is intended to be a replacement therapy for MBL-deficient patients. As a result, with Phase I trials complete, Helion Biotech has identified the prevention of neonatal sepsis as an attractive option for rhMBL. Furthermore, rhMBL was shown to be not active against H1N1 influenza virus infections (see research plan). Our innovation differs from rhMBL as it is genetically-modified and shows broad-spectrum potency against a number of virus strains with strong preliminary efficacy results against the flu. Furthermore, will continue to optimize dosing and formulation with the goal of treating severely ill patients suffering from influenza A and B.

Despite reformulation approaches, NIs continue to suffer from increasing pandemic strain resistance. Future differentiation strategies are reflected by competitor therapeutics in advanced clinical development. Similar to H84T, they target different aspects of the viral replication cycle through novel mechanisms. We also see a trend toward the development of new vaccines to keep pace with the new influenza strains that are emerging, but there are comparatively fewer antiviral therapeutics in the development pipeline, thus creating a unique opportunity for TSRL Inc.’s antiviral products. *We believe there is substantial market opportunity for a novel, broad-spectrum antiviral drug with high potency and low risk for resistance development– and H84T has the potential to display these characteristics.*

**Table 6**. Select Antiviral Therapeutics in Advanced Clinical Development

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Agent | Sponsor | Technology/ Target | Phase | ROA | Pros | Cons |
| Zanamivir | GSK | NI\* | III | IV | Higher systemic exposure; better for critical patients | Invasive; resistance concerns |
| Laninamivir | Biota, Daiichi-Sankyo | NI | III† | Inhaled | Single dose administration; prevention & therapy | Bronchospasm side effects; inhaler needs practice; difficult for ill patients; resistance developing |
| Oseltamivir | Roche | NI | III | IV | Higher systemic exposure | Invasive; resistance concerns |
| Alinia | Romark | Pyruvate-Flavodoxin Oxidoreductase; HA receptor | III | Oral | ROA better for adherence; unique mechanism; prior approval for other pediatric anti-infection indications | Untested mechanism for influenza; may not be suitable for patients with hepatic/renal impairment |
| Favipiravir | Toyama | Inhibitor of viral polymerase | II-III | Oral | Broad-spectrum; route beneficial for adherence | Safety concerns; resistance concerns |
| VX787 | Vertex | Inhibitor of viral polymerase | II | Oral | ROA better for adherence; unique mechanism | Possibility of resistance |
| Ampligen | Hemispherx Biopharma Inc | 2',5'-Oligoadenylate Synthetase (OAS1), Toll-Like Receptor 3 (TLR3) | II | Intra-muscular, Nasal | Broad-spectrum; synergist with existing vaccines | Invasive ROA; efficacy tied to vaccine adjuvant |
| rhMannose Binding Lectin | Helion Biotech | Mannose-binding lectin | I | IV | Broad spectrum binding ability | Invasive ROA; efficacy unknown |

*\*NI=Neuraminidase Inhibitor; †Licensed in Japan; ROA=Route of Administration (Source: Medtrack 2015)*

***Intellectual Property (IP) Protection***

The H84T invention is protected by US Utility patent #8,865,867 issued on 10/21/14 termed “Lectins and Uses Thereof” and has one pending provisional patent application. As stated above, the issued patent includes both composition of matter and method of use claims. We have negotiated a cooperative research and development agreement (CRADA) with Virule, an affiliate asset LLC co-owned by the inventor of the H84T technology and TSRL. Virule will take an option from the University of Michigan, who currently owns the IP, for co-development of H84T with TSRL (see attached letter of intent). Likewise, we have international patent protection through application PCT/US2011/031895 with entry into China (4/11/11), EU (11/13/12), and the US (11/27/12). The parent patent has an expiry of 11/27/32, not including Hatch-Waxman extensions, allowing our development Sponsor sufficient time for commercialization. In addition, there is a continuation-in-part patent application that protects the discovery of the atomic structure that leads to loss of mitogenicity with the retention of lectin antiviral activity. We believe this IP protection, coupled with data exclusivity acquired from the drug development process, will sufficiently prevent competitors from commercializing a similar invention.

***Finance Plan***

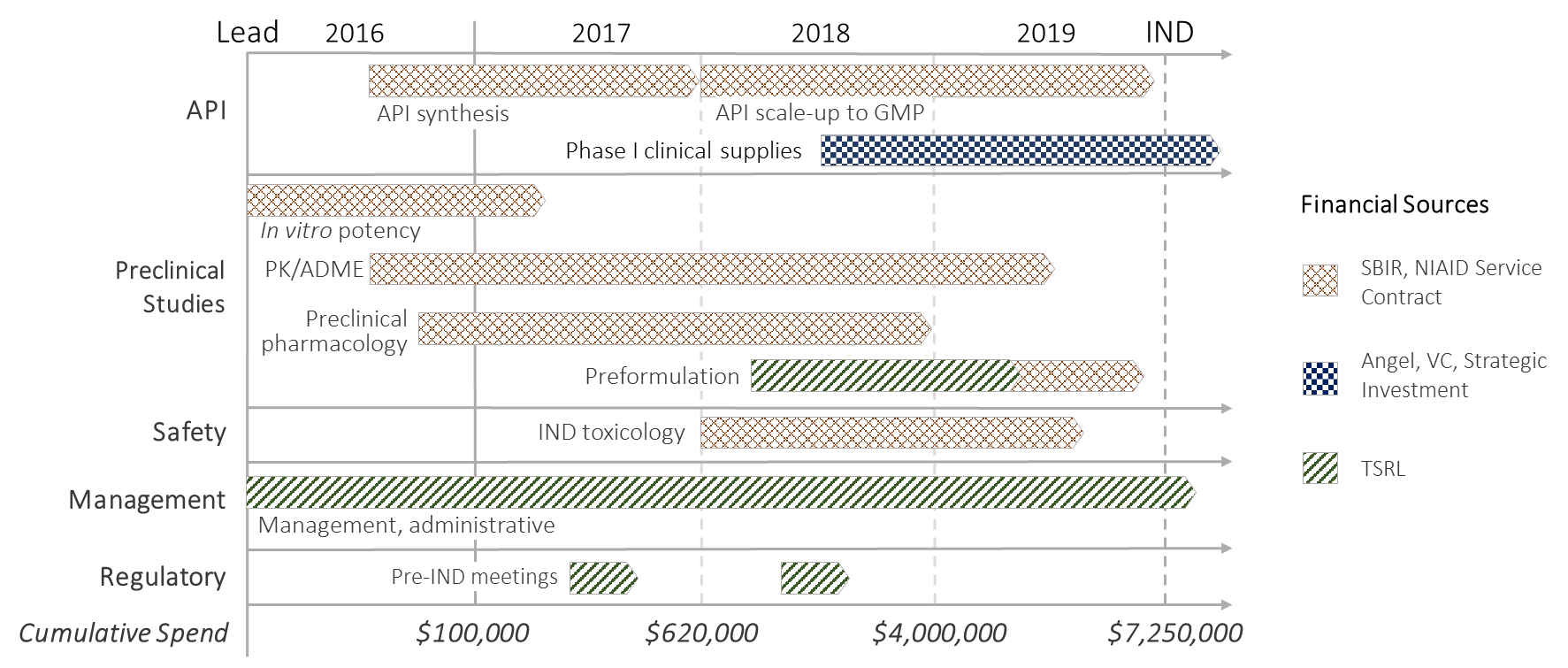
We expect significant costs associated with preclinical development of H84T (**Table 7**). First, our affiliate LLC acquires rights to the IP upon award of the Phase II grant. Upfront IP acquisition costs typically include incurred patent expenses and issuance fees in addition to annual license fees and revenues of net sales post-commercialization. Terms of the initial license negotiation are typically passed through to the Sponsor who would complete the development of the drug. Financing for preclinical development of the H84T asset is provided through grant awards and retained earnings from TSRL’s prior licensing revenue. Specifically, grants support animal studies, some toxicology, and manufacturing scale-up (**Figure 5** shows a sample development plan). It is important to note that there will be additional clinical expenses if we develop the asset past IND.

*\*Does not include technology transfer or license acquisition fees*

**Table 7**. Preclinical Development Expenses\*

|  |  |  |  |
| --- | --- | --- | --- |
| ***Activity*** | **2017** | **2018** | **2019** |
| *Manufacturing* | $150,000 | $1,450,000 | $1,500,000 |
| *Preclinical Studies* | $200,000 | $800,000 | $200,000 |
| *Safety/Toxicology* | $0 | $300,000 | $800,000 |
| *FDA Fees* | $50,000 | $50,000 | $0 |
| ***Expenses Sub-total*** | **$400,000** | **$2,600,000** | **$2,500,000** |
| *Admin/Overhead (%30)* | $120,000 | $780,000 | $750,000 |
| ***Total Expenses*** | **$520,000** | **$3,380,000** | **$3,250,000** |

**Figure 5**. Preclinical Development Plan with Financing Sources



***Production and Marketing Plan***

***Production***: TSRL will outsource production of drug product and formulation to contract manufacturing organizations (CMOs). We are in the process of receiving quotes for the initial early clinical stage scale-up (up to 1 kg) activities from vendors such as Paragon Biosciences, Octoplus and CMC Biologics. Cost of goods sold (COGS) will be higher for biologic scale-up of H84T due to direct and indirect costs associated with growing recombinant protein in large-scale *E.coli* fermenters. For a separate program, CMO Leidos estimated costs of $1 million for production of ~750g GMP protein at the 1000L scale. Using 100mg/dose as a benchmark, this is equals $133 in API COGS/dose. We up-mark this 200% to $266/dose to take into account finished product/formulation costs, while assuming economies-of-scale (10,000L+) also reduce COGS. As a result, we believe H84T as a therapeutic protein would fall between $200-400 in COGS at the commercial scale. This represents a 40-50% profit margin when taking into account wholesale mark-up.

Higher COGS are likely to be offset by price premiums paid as a result of higher demand; severely ill patients will require H84T as drug of last resort and the reimbursement landscape will reflect this. For example, Rapivab™, the only intravenously available treatment for severe influenza, has a wholesale acquisition cost of $950 per dose. It is available as a 200 mg/20 mL single use vial with three vials making up the standard 600 mg dose [24]. Our estimated price point ($1000) is in line with Rapivab™, driven by willingness of customers to pay for lifesaving treatment. However, as we develop our pricing strategy and dosing regimen we will perform a QALY analysis to determine likelihood of reimbursement in select markets and adjust pricing accordingly. Although CMS does not provide National Coverage Determination, many commercial payers provide coverage and sponsored copay savings programs exist to cover the majority of out-of-pocket costs.

***Marketing***: Marketing activities occur post-out-license or acquisition by a clinical sponsor after a New Drug Application (NDA) is approved by the FDA. However, our strategy is to engage industry early in the process while we gather critical safety and efficacy data. As a drug product’s key properties and label claims are defined by what data is generated in clinical trials (and pre-positioned in pre-clinical studies), TSRL has already thought through the overall approach of positioning our anti-influenza program in the likely future competitive environment. We have put together an initial target product profile that addresses our target market (**Table 8**).

**Table 8**. Target Product Profile for H84T Antiviral

|  |  |  |
| --- | --- | --- |
| Attribute | H84T Must Have | Ideal Drug |
| Resistance Frequency | Limited resistance development | Limited resistance development |
| Indications | Treatment of Influenza A and B in severely ill patients | Treatment of all influenza strains; other respiratory viruses in severely ill patients |
| Target Population | Hospitalized adults | Hospitalized adults and children; ability for prophylaxis in a wider population |
| ROA/Dosage frequency | IV; 1-3 times per treatment | IV; once per treatment |
| Safety | As safe as Rapivab® | As safe as Rapivab® |

Depending on our capabilities and fundraising circumstances, we may complement internal investment with outside capital raised from angel investors or venture capital firms to enter the clinic ourselves. In this scenario, we realize significant value by driving clinical trials internally to the next value inflect point, often proof-of-concept (POC) in humans. A more defined product profile will emerge as we continue our market research efforts and will lead to a stronger negotiation position for acquisition discussions with a commercial sponsor.

***Revenue Stream***

As stated above, we position our affiliate LLC for an exit via out-license or acquisition. For both exit scenarios we use industry comparables as well as a bottom-up market approach to capture potential deal structure. In the out-license scenario, revenue is generated in the short-term through equity consideration, reimbursement for upfront technology and R&D costs, and near-term milestone payments. Longer-term revenue streams consist of developmental and sales milestones, sublicense revenue, and royalties on net sales. For the acquisition scenario, we would likely develop the asset past-IND to POC in humans with the goal of a major lump sum acquisition by a sponsor. To address this, we have conducted an analysis of industry licensing deals pre-POC and post-POC supplemented by data obtained from a Licensing Executives Society (LES) survey [25].

We performed a financial modeling analysis for a licensing scenario post-IND and pre-POC(**Figure 6**)**.** With this approach wemade conservative assumptions knowing adoption and penetration would be limited with an IV therapeutic (**Table 9)**. Industry comparables were used as guidance. To begin, median lump sum payments for technology access and R&D funding total $1.4 million for deals at pre-POC upon signing. Additional development and sales milestones at this stage have historical medians of $3.0 million and $2.2 million, respectively. After POC in humans (Clinical Phase 2a), deal terms become significantly more favorable. For instance, Vertex Pharmaceuticals licensed influenza therapeutic VX-787 for $30 million in upfront milestones and an undisclosed royalty rate to Janssen Pharmaceuticals in 2014 [26]. Likewise, royalties of net sales of preclinical assets at pre-POC average 6% and increase further down the development pipeline. A deal between Biota Holdings, original developer of Relenza, and sponsor GlaxoSmithKline negotiated a royalty rate on net product sales of 7% at Phase II [23]. In an acquisition scenario, which is not detailed here, our asset would be acquired as a single, lump sum deal with immediate return on investment post-POC.

**Figure 6.** Projected Affiliate LLC Net Cash Flows from H84T Deal Post-IND/Pre-POC

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Preclinical | Preclinical | Phase I | Phase II | Phase III | Review | Ramp-Up | Ramp-Up | Plateau |
| ($ in thousands) | *2015/2016* | *2017/2018* | *2019/2020* | *2021/2022* | *2023/2024* | *2025/2026* | *2027/2028* | *2029/2030* | *2031/2032* |
| Sponsor Product Revenue | $0 | $0 | $0 | $0 | $0 | $0 | $644,156 | $434,663 | $354,295 |
| Asset LLC Dev Costs | $520 | $6,630 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| Payments to U of M | $136 | $125 | $630 | $500 | $550 | $550 | $13,883 | $8,693 | $7,086 |
| Payments from Sponsor: |  |  |  |  |  |  |  |  |  |
| Milestones | $0 | $0 | $1,900 | $1,000 | $1,000 | $1,000 | $2,200 | $0 | $0 |
| % Net Sales (6%) | $0 | $0 | $0 | $0 | $0 | $0 | $38,649 | $26,080 | $21,258 |
| Net Cash Flow | ($656) | ($6,755) | $1,270 | $500 | $450 | $450 | $26,966 | $17,387 | $14,172 |

*A novel influenza therapeutic with a higher potency and superior antiviral resistance profile peaks at over $300 million/year in sales revenue for our sponsor and over $20 million/year in royalty revenue for our affiliate LLC, driven by government stockpiling*. These are estimates for the severe influenza indication, not including additional markets (on and off-label) made possible by the broad spectrum nature of the therapeutic, so total revenue figures over time could be much higher.

**Table 9.** Major Assumptions for Revenue Projections [25]

|  |  |
| --- | --- |
| * Upfront milestone $1.4m post-IND * Further development milestones totaling $5.2m * License to sponsor post-IND (pre-POC) * Preclinical phase takes 3 years, to be done by TSRL * Flat rate royalty paid by sponsor 6% product revenues * 20% sublicense consideration and flat royalty 2% product revenues paid to collaborator * Adoption reaches peak 6 years post-launch | * Market includes USA, JAP, and EUR * Peak market penetration of 15%, significantly less than available oral products * Revenues average of pandemic and seasonal sales estimates times population growth * Sales decrease after initial stockpiles efforts * Vaccines consume 20% more market share due to increased coverage and efficacy of new offerings |

Long-term sustainability for TSRL’s operations derive from development and sales milestone payments, royalty income from antiviral products, and ROI from investment in asset LLCs. We continue to investigate new drug therapy concepts by collaborating with investigators from industry and academia in the preclinical space. As a drug development accelerator, it is our goal to de-risk and advance drug therapies for addressing unmet needs in populations suffering from infectious diseases. Eventually we plan to grow into a clinical-stage development company and diversify our product portfolio to develop candidates for a variety of therapeutic indications. At that point, we will recruit additional individuals with fundraising, regulatory, sales, marketing and leadership experience. In the meantime, we will continue to engage our network of key opinion leaders, consultants, and advisors.

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