

# **Ligeia Business Plan**

## **Harvard Biotechnology Club Business Plan Competition**

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## LIGEIA EXECUTIVE SUMMARY

Ligeia is a drug discovery company whose first lead compound will provide a small-molecule therapeutic solution for the \$1.4 billion market related to Human Papilloma Virus (HPV) infection. Our technology relies upon a novel use of the proteasome to degrade disease-causing proteins and reveal infected cells to the immune system. There is an unmet need for our product, as current HPV therapies are expensive, invasive, and inconvenient.

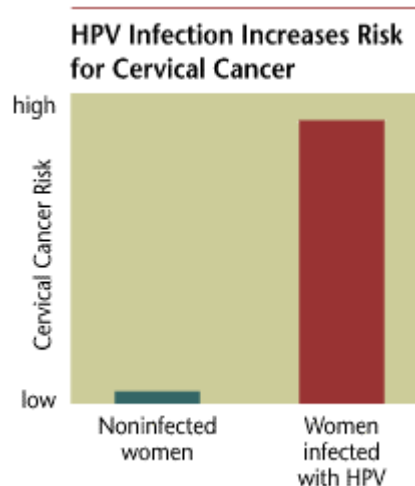
- **The Problem:** HPV is the most widespread STD in the US, infecting 5.5 million people each year, and is causal in 99% of cervical cancers. Current treatments for HPV are costly, ineffective and invasive. There is an unmet need for a non-invasive therapeutic cure for the millions of women who are infected with HPV.
- **The Solution:** Our lead compound will neutralize HPV infection by targeting HPV E7 protein to the proteasome for degradation, consequently facilitating the removal of infected cells by the immune system. This small-molecule therapeutic is based on patent-pending technology developed in George Church's lab at Harvard University.
- **The Market:** Datamonitor estimates a global market for an HPV therapeutic of \$1.4 billion. Ligeia will initially target the US market for women infected with "high-risk" subtypes of HPV. We estimate this initial market to have a size of \$350 million annually. This market can be expanded to include lower-risk subtypes and other geographies.
- **The Competition:** Currently there is no therapeutic cure for HPV. However, there are on-going development programs for both HPV therapeutics and an HPV vaccine (programs on-going at GSK and Merck). The presence of these competitive efforts indicates that there is indeed an unmet market need for HPV treatments.
- **Ligeia's Competitive Advantage:** Ligeia's therapeutic will rely upon a novel mechanism of drug action, which will both degrade viral proteins as well as stimulate the immune response. Our lead compound will follow a small-molecule formulation, decreasing both costs and increasing likelihood of patient/physician adoption. Our compound will also have lower dosage needs due to its catalytic action.
- **Business Model:** Recognizing the difficulty in bringing a single product to market, Ligeia will focus its efforts primarily upon product R&D and co-product development, and rely upon our experienced partner for manufacturing, sales, and distribution. Ligeia's core technology is extendable to other major viral diseases, and in the future the company will focus on building a portfolio of small molecule drugs for their treatment. We anticipate funding needs of \$2 million for the first year of operations.
- **The Team:** The company has in place an outstanding team with scientific, operational and legal experience. We believe our team is well suited for management at the initial seed and early R&D funding stages. Beyond that, as Ligeia's technology develops it will become critical to recruit an experienced life-science executive to take the reins as CEO and lead Ligeia further into clinical development and partnerships with large pharma.

# THE PROBLEM

## HPV is a major health challenge

Human Papilloma Virus (HPV) is the most common sexually transmitted disease in the United States. About 24 million Americans are currently infected with HPV, with an estimated 5.5 million additional infections each year. 4.6 million of these cases are acquired by young Americans between the ages of 15 and 24. Infection with high-risk HPV subtypes (16 and 18) is causal in over 99% of cervical cancers. More than 50% of women are infected with high-risk strains.

HPV infection is also associated with other cancers and more than one million pre-cancerous lesions. Infection with low-risk HPV subtypes can lead to the development of highly contagious genital warts. The total medical costs of treating HPV infection and its complications are estimated to be from \$3 billion to \$6 billion in the US alone each year.



*Women infected with high-risk subtypes of HPV are at greater risk for cervical cancer*

## There is no cure for HPV

There is currently no cure for HPV available on the market. Therefore once infected, a person is likely to carry the virus for life. In most cases an active infection is controlled by the immune system and with time becomes dormant; however, it is not possible to predict whether or when the virus will become active again. The only treatment available now involves either physical removal of infected cells using an invasive procedure such as surgery, or harsher treatments such as chemotherapy or radiation therapy. This also requires constant monitoring through the form of annual checkups.

## **Existing treatments are expensive and invasive**

Over 1,350,000 women will have invasive procedures each year just to assess the status of their abnormal pap smears secondary to HPV. According to the American Cancer Society, every year over 12,000 new cases of invasive cervical cancer are diagnosed and more than 4,000 women die of the disease. Non-invasive cervical cancer is estimated to be four times as widespread as the invasive type. The direct medical cost of treating a patient with cervical cancer is \$9,200 to \$13,360, while surgery to remove a pre-cancerous lesion is \$1,100 to \$4,360. Side effects of treatment include pain, scarring and the loss of fertility through the removal of the uterus.

## **Patients suffer emotional consequences**

Due to the invasive nature of current treatment and the associated risks involved, after the first positive test result, doctors and patients wait 4-6 months before retesting for the presence of abnormal cervical cells. If the test is positive the second time, a further invasive test, a colposcopy is performed. Only then will the doctor recommend further surgery. During this waiting period patients suffer the emotional consequences of being a carrier and also risk infecting others.

# **THE SOLUTION**

## **E7Deg will solve the problem with a pill**

Our first development program, E7Deg will provide a small-molecule therapeutic cure for HPV infection. Ligeia's solution will be an attractive alternative to the expensive and invasive surgery currently employed in treating health problems related to HPV infection. This is made possible by our patent-pending technology, which allows the development of therapeutic drugs that are more likely suited for pill formulation.

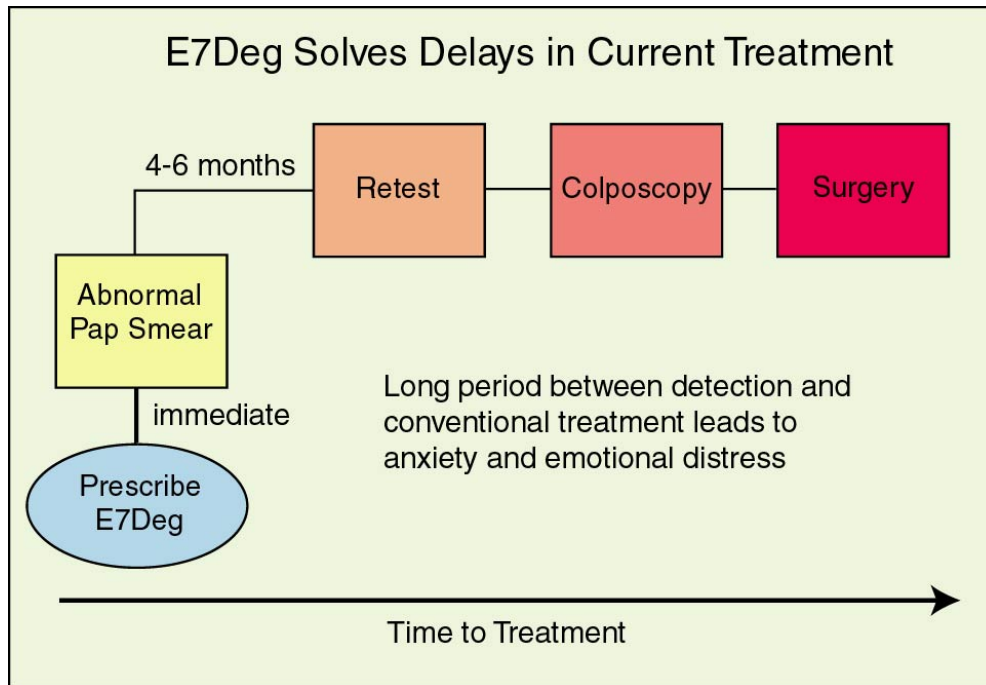
Ligeia's solution will radically alter the treatment of HPV by giving physicians a tool to eradicate infection. Administration will now be safe, convenient and managed by the patient. Our product will be in high demand, as it will increase the quality of life for patients with respect to HPV treatment.

## **E7Deg will be effective at all stages of infection**

Ridding the virus from the body is the only sure means for halting disease progression. E7Deg specifically targets and facilitates the destruction of infected cells. Therefore, we anticipate our product will be effective against the full spectrum of HPV related diseases: from primary infections, to the onset of cervical dysplasia, to cervical cancer.

## E7Deg will access an untapped patient population

Due to the invasive nature of surgery, after the initial diagnosis with HPV both physicians and patients often wait for abnormal cervical cells to manifest before resorting to operation. Confirmation usually takes an additional four to six months. During this time, patients often experience unwanted anxiety, stress and strong feelings of shame. The reduced risks associated with E7Deg means that women would no longer have to delay treatment. E7Deg may be prescribed immediately upon diagnosis.



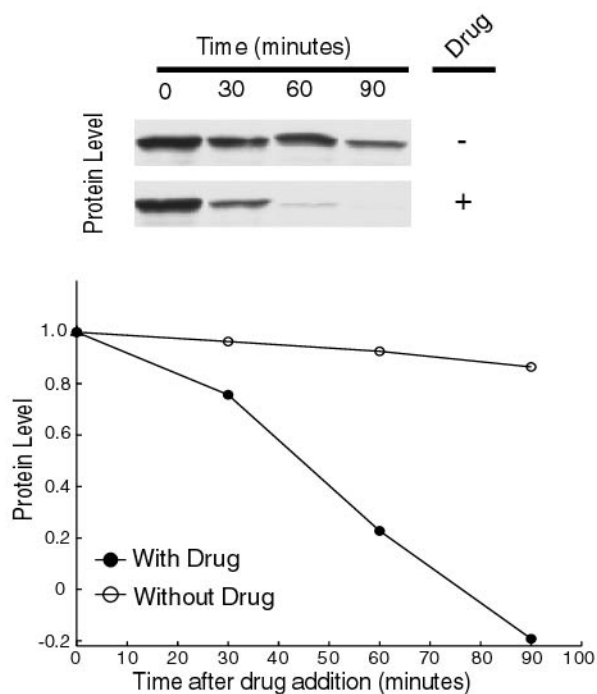
*E7Deg is safe and non-invasive and may be prescribed immediate upon detection of abnormal cells. This eliminates the stress patients feel waiting for retesting.*

## THE PRODUCT

Ligeia's main value stems from its proprietary technology platform, which allows for the discovery of small-molecules drugs effective in the treatment of viral diseases and cancers. Our initial development program, E7Deg, will treat individuals suffering from diseases related to HPV infection. E7Deg will work in concert with the host immune system to rid the body of the virus. Its novel mechanism of action forms the basis of Ligeia's patent-pending technology.

### Proof of principle has been demonstrated

Ligeia's core technology was developed by Daniel Janse in the laboratory of Professor George Church at Harvard Medical School. Using a small-molecule that bound on one face to a target protein, and on the other face to the proteasome, Mr. Janse demonstrated that the cell's normal mechanism for protein degradation could be bypassed, and that artificial localization of the target to the proteasome was sufficient for degradation. This is a general phenomenon and will allow Ligeia to pursue many different disease-causing proteins. The work described here has been peer reviewed and published in the Journal of Biological Chemistry<sup>1</sup>. In addition, it has been disclosed in a provisional patent application. Mr. Janse is a member of Ligeia's founding team and an author of the pending-patent covering the core technologies.



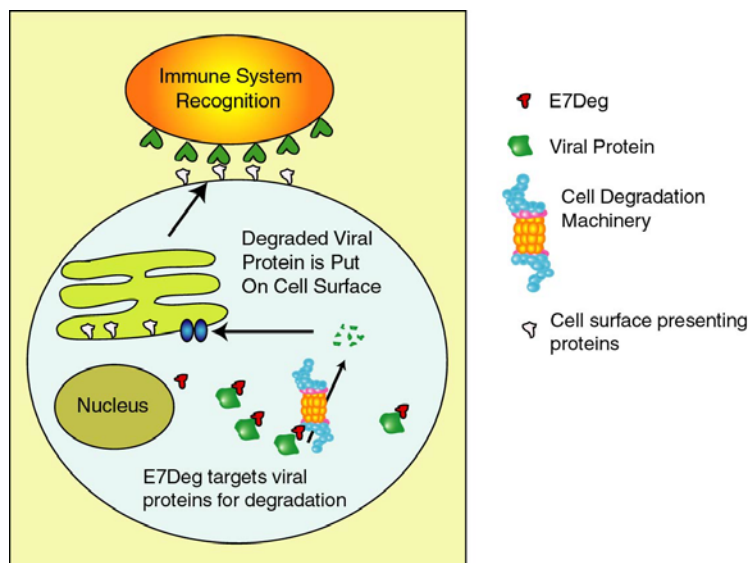
*Proof of principle was demonstrated on a test protein. In the presence of the drug the protein is degraded rapidly, as compared the same preparation without the drug.*

## High Throughput Platform being developed

Advances are currently being made to develop a High Throughput Drug Discovery Platform. This work is being done in collaboration with Dr. Angela Koehler and Professor Stuart Schreiber at Harvard University. The platform will exploit the power of traditional chemical library screens to identify small molecule binders of disease-causing proteins. Importantly, we anticipate a higher hit-rate as compared to screens for inhibitors of the same proteins, as we only require that a binding event occur, without any inhibitory consequences. Once identified, binders will be crosslinked to Ligeia's proprietary proteasome-binding molecule to create a functional lead compound capable of localizing the target protein to the proteasome. For this purpose we have designed universal crosslinkers that will conjugate any two members of our chemical library. Beyond our first development program for HPV, the flexibility of the platform technology will allow Ligeia to build a portfolio of drugs, targeting additional viral-mediated diseases such as Hepatitis C, as well as certain types of cancers.

## E7Deg will destroy HPV viral proteins and rid it from the body

E7Deg promotes the destruction of infected cells by degrading viral proteins and signaling the immune response. HPV evades immune detection by down-regulating the presentation of viral proteins on the cell surface, thus causing the immune system to not recognize that a cell is infected. Antigen presentation is proportional to the availability of degraded viral fragments. The mechanism of E7Deg action enhances the presentation process. E7Deg will bind to and target the disease-causing HPV E7 protein to the proteasome, consequently increasing the pool of degraded E7, and thus the amount of E7 antigen presented on the cell surface. As a consequence of presentation, the host immune system is alerted and destroys the infected cell.



*E7Deg enters infected cells, specifically binds HPV E7 protein and targets it to the proteasome. Once degraded, the cell naturally presents the viral peptides on the cell surface. The immune system can now recognize that the cell is infected and destroy it.*

# MARKET ANALYSIS

## 5.5 million people are infected by HPV each year

The National Institutes of Health (NIH) estimates that approximately 24 million Americans are infected with HPV, with roughly 5.5 million new infections each year. Recognizing the increased risk of developing cervical cancer associated with infection, 3 million women undergo Pap smear testing annually. As a result, roughly 600,000 of these women are diagnosed with cervical dysplasia and a further 12,000 with cervical cancer. HPV infections are classified by a number of subtypes of which two (HPV-16 and HPV-18) are considered to be the highest risk for developing cervical complications. Roughly 50-75% of HPV infections are by these “high-risk” subtypes.

## The estimated market size for this product is \$1.4 billion across the seven major markets

Market research<sup>2</sup> from Datamonitor suggests that the market for an effective treatment based on current epidemiological trends and pricing benchmarks for other viral treatments, could generate annual sales of \$1.4 billion. This project includes accounting for a successfully developed prophylactic vaccine.

## Ligeia will initially target the US market for women infected by high-risk HPV subtypes

US Incidence of HPV Infection:		5.5 million / year
US Incidence (Female):		2.75 million/ year
Infection by HPV “high-risk subtypes:”	60%	1.4 million
Diagnosed:	50%	700,000
Seeking Treatment:	50%	350,000
Annual treatment costs:		\$1,000
Total initial target market size:		\$350 million

## Current estimated costs for treatment of HPV in the US are nearly \$3 billion

Over 80% of all new infections occur in young adults aged 15-24. As a result, 1.4 million women undergo invasive testing each year, in response to abnormal pap smears. According to a year 2000 CDC study<sup>3</sup>, the estimated direct medical costs are \$2.9 billion, for this age group alone. This includes costs due to treatment of HPV complications, such as cervical cancer and anogenital warts as well as the need for follow up Pap tests.

## E7Deg meets an unmet need in the marketplace

HPV is one of the greatly understated public health needs in the US, accounting for half of all STD infections each year. Direct medical costs are on par with those for HIV-infected individuals. This has attracted the attention of several large pharmaceutical firms and efforts to develop effective vaccinations. Regardless of whether these development programs are successful, there remains a need for a simple therapeutic that is curative for HPV infection.

# THE COMPETITION

## Competition validates market

There is no therapeutic cure for HPV-infected individuals currently on the market. However, several biotechnology and pharmaceutical companies are trying to develop therapies to address the unmet market need for affordable, non-invasive and convenient treatments.

## Current Solutions are not Attractive

Currently, most early-stage infections are simply monitored and left untreated. More severe cases are treated by a combination of surgery, chemotherapy and radiation therapy - expensive and invasive procedures that are frequently accompanied by debilitating side effects including pain, scarring and the potential loss of fertility. The direct medical cost of treating a patient with cervical cancer is \$9,200 to \$13,360, while surgery to remove a pre-cancerous lesion is \$1,100 to \$4,360.

## Direct competitors are developing therapeutics

Therapeutic treatments are intended to cure HPV infections. Ligeia will compete directly with Zycos, Epimmune and Stressgen. Our direct competitors' approach is to generally enhance the immune response towards HPV infected cells. This is accomplished by introducing non-infectious virus proteins to the body via DNA and protein based formulations. The immune system processes these proteins, identifies them as foreign and then mounts a response to target infected cells that also carry those proteins.

Each competitor is in various stages of development as shown in Table 1:

Company	Product	Development	Partner
<b>Zycos</b>	ZYC101a	HPV - Phase 2b completed Cervical Dysplasia – Phase 3 to start Genital Warts – Phase 2 to start	None
	ZYC101b	HPV – in development (no clinical work)	
<b>Epimmune</b>	CIN/Cervical Vaccine	Pre-clinical	Genencor
<b>Stressgen</b>	HspE7	Anal Dysplasia – Phase 3 completed Cervical Dysplasia – Phase 2 ongoing	Roche

Table 1: HPV Therapeutic Solutions of Direct Competitors

### Indirect competitors are developing vaccines

Prophylactic vaccines are intended to prevent HPV infections. Ligeia will compete indirectly with Merck, MedImmune and GSK. These companies are testing products for the prophylactic vaccine market. Vaccines work by priming the immune system for future infections. All our indirect competitors use a similar approach. Non-infectious HPV virus-like particles (VLPs) are introduced to the body, causing the immune system to produce antibodies that recognize HPV. In the event of an infection, the immune system is already primed to neutralize the disease-causing virus.

Several prophylactic vaccines are currently in clinical trials as shown in Table 2:

Company	Product	Development	Partner
Merck & Co.	HPV Vaccine	Phase III – ongoing Plan to file for FDA approval in late 2005	None
MedImmune	HPV Vaccine	Phase II – ongoing	GSK
GSK	Cervarix	Phase II – ongoing	None

Table 2: HPV Prophylactic Solution of Indirect Competitors

### RNAi is not a valid competing technology

The possible use of RNAi as a therapeutic has recently garnered a lot of attention. RNAi works by destroying mRNA, the precursors of target proteins. Currently there are no RNAi therapeutics in clinical trials. The field still has significant hurdles to address before RNAi becomes a viable therapeutic product. The major issues that have not been solved include stability, specificity, delivery and potency. RNA based therapies are not new, two other technologies (ribozymes and antisense) created big splashes when they were first reported but since have not made significant inroads into the therapeutics market. The two largest therapeutic RNAi companies are Alnylam and Sirna. RNAi technology does not pose an immediate threat to Ligeia.

## COMPETITIVE ADVANTAGE

Ligeia’s solution provides real advantages over its competitors. Our novel immunotherapeutic strategy specifically targets HPV infected cells by utilizing a two-pronged approach: degrading viral proteins and specifically alerting the immune system to destroy infected cells. Below is a table that summarizes Ligeia’s major advantages over its competitors in terms of efficacy, cost and patient preference.

	<b>Competitors</b>	<b>LIGEIA</b>
<b>Drug Mechanism</b>	<i>General</i> enhancement of immunity	<i>Specific</i> targeting of infected cells
<b>Formulation: Cost</b>	Protein/DNA: Higher Costs	Small Molecule: Lower Costs
<b>Administration</b>	Injection	Pill Form

*Table 3: Ligeia’s solution provides real advantages over its competitors*

### **Prophylactic vaccines will not cure the 300 million people already infected**

Widespread use of a proven prophylactic vaccine will eventually minimize the need for therapeutic treatments in the long term. However, historically, mass adoption of a vaccine has taken 20 to 30 years after its introduction. Furthermore, in the absence of specific immunization regulation, adoption rates may fluctuate widely and leave a substantial size of the population unprotected, and in need of therapeutic treatment. Lastly, vaccines are preventative and thus not effective for the more than 300 million people already infected the globally.

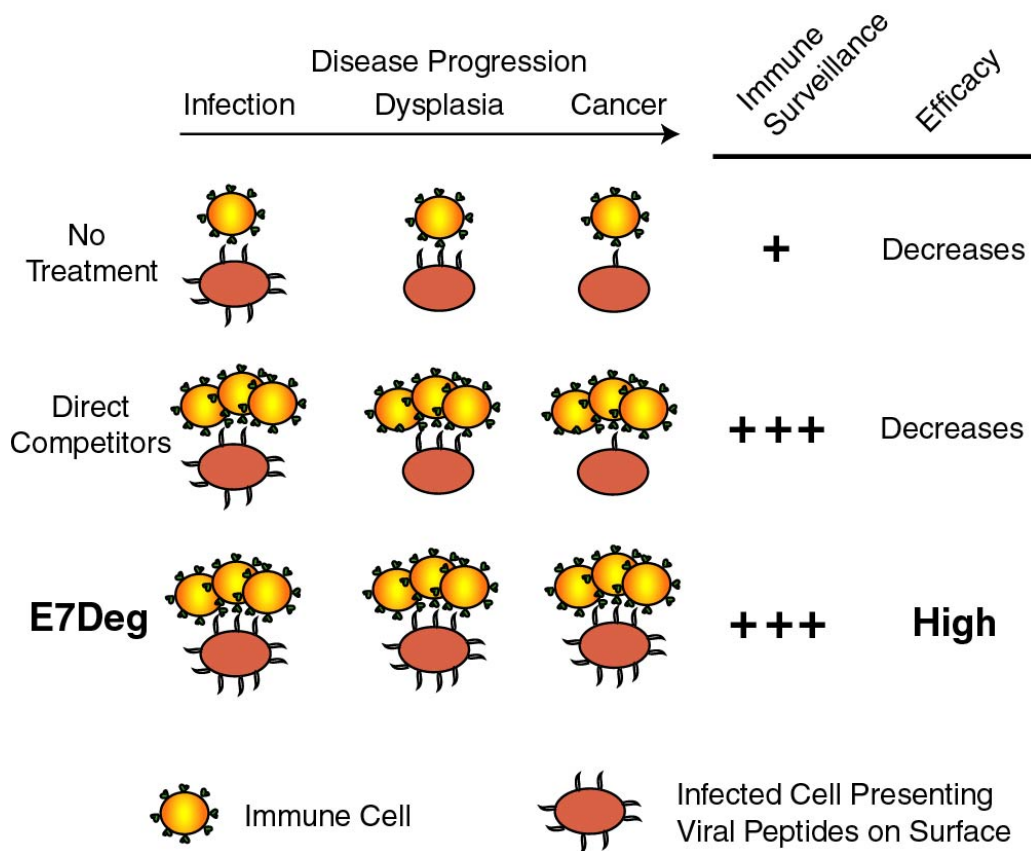
### **Efficacy of prophylactic vaccine questioned**

Recently the efficacy of the vaccine closest to market, Merck's lead candidate, has been questioned. Changes during a woman’s menstrual cycle may affect the production level of antibodies to HPV. Furthermore, it was also shown that antibody levels decrease over time, which would require that patients receive repeated vaccinations (as often as once every two years) over their lifetime. The small study<sup>4</sup> was published in the Journal of the National Cancer Institute in 2003.

## Direct competitors do not unmask infected cells

Persistence of HPV infection and progression of disease is a result of the viruses' ability to evade the immune system. One mechanism HPV employs, is to down-regulate the ability of an infected cell to present viral peptides on its surface. Without viral peptides on the cell surface, the immune system is unable to recognize the cell as infected. Therefore in these cases, therapeutic strategies such as our competitors', which merely boost the immune system, will exhibit decreasing efficacy with disease progression.

Ligeia's small molecule solution is better. E7Deg degrades viral proteins, and thus will *maintain high levels* of viral peptide presentation on the cell surface. Our unique mechanism for targeting disease proteins will provide effective treatment for all stages of disease progression, from initial infection, to cervical dysplasia and cervical cancer.



*As disease progresses from infection to cancer, the virus hijacks the infected cell and makes it less visible to the immune system. The reduced number of viral peptides on the cell surface illustrates this above. Our direct competitors try to boost the immune system to address this, which is decreasingly effective with disease progression. E7Deg increases the detection of infected cells by increasing the presentation of viral peptides. This effect feeds back and also increases the immune response.*

### **E7Deg costs less**

Currently, the direct medical cost of treating a patient with cervical cancer is \$9,200 to \$13,360, while surgery to remove a pre-cancerous lesion is \$1,100 to \$4,360. Ligeia and its competitors seek to reduce these costs by offering inexpensive pharmacological alternatives. Ligeia has an added advantage over its competitors because of our small molecule formulation. Compared to DNA and protein formulations, Ligeia will enjoy decreased overheads on the order of five to ten-fold associated with manufacturing, transport, and storage.

<b>Company</b>	<b>Product Type</b>	<b>Costs</b>	<b>Convenient</b>
Merck	Prophylactic	High	No
GSK	Prophylactic	High	No
Medimmune	Prophylactic	High	No
Zycos	Therapeutic	High	No
Stressgen	Therapeutic	High	No
<b>Ligeia</b>	<b>Therapeutic</b>	<b>LOW</b>	<b>YES</b>
Epimmune	Therapeutic	High	No

*Table 4: Ligeia's solution costs less and is more convenient than competitors*

### **Patients prefer pills over injections**

Patients will demand our product because E7Deg will be effective in curing HPV infection, they will not have to wait 4-6 months for retesting, and we anticipate E7Deg will be available in a pill form. Our direct competitors will use DNA and protein based formulations, which means that they will only be able to offer administration through injections. Further advantages that pills have over injections are that patients will be able to complete their prescriptions at home, and dosage will be spread out over time, rather than being administered as one large bolus.

### **We anticipate E7Deg will be safer**

Most small-molecule drugs work in a one-to-one manner; one drug molecule inhibits one protein. We expect E7Deg to work catalytically; once a protein is bound and degraded by E7Deg, our drug is free to seek out more viral proteins. Because of this we anticipate E7Deg will be efficacious at lower concentrations, which translates to increased safety and lower occurrences of side effects.

## THE COMPANY

Ligeia is currently securing intellectual property rights for the technology platform and recruiting professional management. In the near future we do not envision evolving Ligeia into a fully integrated biotechnology company due to the tremendous costs and risks involved. Rather we seek to capitalize on the need for established biotechnology firms to expand their offerings. We believe we can fully meet this need with Ligeia's technology platform. Thus, for the near future we envision Ligeia as dedicated to the discovery of lead compounds.

By the end of the 2004/Q2 Ligeia plans to have performed the following key functions:

- Finalize discussions with the Harvard Medical School Office of Technology Licensing (OTL) about licensing patents relevant to Ligeia's technology platform
- Begin negotiations with investors
- Start recruiting an experienced CEO

### Ligeia will license E7Deg technology from Harvard Medical School

A provisional patent application describing Ligeia's core technology has been filed with the U.S. Patent and Trademark Office. Ligeia has initiated negotiations with Maryanne Fenerjian from the Harvard Medical School Office of Technology Licensing (OTL) for an exclusive license. OTL has agreed to furnish Ligeia with a Letter of Intent and not seek other partners while Ligeia finds sources of funding. Ligeia plans to further expand its intellectual property by incorporating the advances being made in collaboration with Dr. Angela Koehler and Professor Stuart Schreiber at Harvard University.

### E7Deg Product Development Timeline

2004/Q2	2005/Q1	2006/7	2007/8	2010 +	2012 +
+ Secure initial funding +Technology Platform Development	+ Funding to initiate pre-clinical animal studies	+ Partnership finalized + Milestone payments received + Phase 1 Clinical Trials start	+ Phase 2 Clinical Trials Start	+ Phase 3 Clinical Trials Start	+ File w/ FDA + E7Deg on Market

There are three key short-term milestones critical to ensuring Ligeia's success:

- Identification of lead compounds for degradation of HPV viral proteins
- Completion of successful pre-clinical animal studies
- Form a development partnership to conduct clinic trials

## **The development partnership**

The substantial financial resources necessary to bring a product through clinical trials necessitate the establishment of a development partnership. Ligeia will seek pharmaceutical partners with a need for E7Deg technology, and infrastructure capable of supporting it. Points of negotiation will include:

- Licensing of intellectual property for E7Deg
- Milestone and royalty payments
- Manufacturing and world-wide licensing rights
- Ownership or participation in future IP generated from Ligeia's core license

## **E7Deg manufacturing – scaleable & safe product**

Should it be necessary, Ligeia plans to subcontract space in a FDA clinical trial Good Manufacturing Practice (GMP) facility to produce pilot scale quantities of our lead compounds, thus minimizing early capital costs. Current batch manufacturing processes can be utilized for our lead compounds to accommodate future large-scale clinical trials. The potential to subcontract space does depend on the course of negotiations with potential partners such as Merck or Pfizer.

## **E7Deg co-refinement, clinical phases**

Ligeia and our strategic partner will initiate E7Deg clinical studies to:

- Demonstrate superiority over existing invasive HPV treatments
- Determine the safety and efficacy in humans
- Determine the optimal dosing and interval

Ligeia's revenue will originate from the following business model:

- Milestone payments (from the partner) during the development of E7Deg
- Royalties from geographic licensing of E7Deg and corresponding sales
- Development and marketing of future compounds based on Ligeia's technology

## **Potential beyond HPV & E7Deg**

Ligeia's core technology is a general method for creating small molecule compounds that act by targeting disease proteins within a cell for degradation. This is a novel pharmacological approach to disease treatment, and will enable Ligeia to pursue diseases that have thus far eluded traditional methods employed by the industry.

Our short-term objective is to deliver sustainable growth by first completing the development work to date on E7Deg, which has an extremely large user base in need of such a solution.

Our long-term solution is based on the discovery potential of our technology platform. Beyond HPV, Ligeia is positioned to develop a portfolio of compounds that target additional viral-mediated diseases such as Hepatitis C, and also certain cancers.

# MARKETING AND SALES

Ligeia intends to enter into strategic partnerships for marketing and sales efforts to commercialize our products. We will focus on identifying suitable partners that meet the following criteria:

- Need or desire to enter or expand into infectious disease and cancer market segments
- Established marketing and sales presence
- Financial resources to support R&D and licensing in favorable terms

## **Most likely partner is a pharmaceutical company**

Ligeia believes that a partnership with a large pharmaceutical company will be the best option for the following reasons:

- They already have an established sales and distribution network
- They have small molecule manufacturing capability
- They have enough resources to commit to a project with a 7-10 year exit horizon

## **Pharmaceutical companies can expand market share with Ligeia's technology platform**

Ligeia's technology platform offers advantages over the competition and will attract interest from companies wishing to have a dominant market presence. The technology platform is capable of generating multiple drug candidates in treating infectious diseases and certain types of cancer. This would be attractive to companies such as Pfizer, Novartis and BMS. They can increase their market share and enter into new market segments. We believe that Pfizer, Novartis and BMS are the best partnership candidates because they already have an established sales network and presence in the market, and can manufacture small molecule compounds. Ligeia's platform will also be attractive to Merck and GSK because their potential HPV vaccines are prophylactic in nature and by including Ligeia's product candidate, E7Deg, they will be able to address the entire HPV market by offering both therapeutic and preventive treatments. For large pharmaceutical firms, Ligeia will highlight the following value proposition:

- Small molecule formulation
- Alignment with partner's current therapeutic focus
- Investing in Ligeia will reduce R&D expenditures

In addition we will emphasize the significant expansion of a partner's offerings in a given market.

## **Value proposition to end customers**

The decision to use E7Deg will be made by physicians. However, we believe that it is equally important to raise awareness about our HPV treatment with patients. These include patients that have been diagnosed with cervical cancer, as well as those that have received an abnormal Pap smear and are required to wait six months before further confirmation. In both cases, we believe physicians may prescribe E7Deg immediately after diagnosis.

## **Patients**

Ligeia envisions our partner marketing directly to the patients and potential customers via promotional ads and using physicians as the primary communication channel. The value proposition needs to highlight the benefits of the product, including:

- Complete elimination of HPV
- Elimination of surgery
- Oral administration (taking a pill) as opposed to regular injections
- Less anxiety, stress and feelings of shame associated with waiting for confirmation

## **Physicians**

The value proposition to physicians will be two-fold:

- Ease of oral administration – no need for injections
- Earlier treatment instead of 6 months waiting period for confirmation of tests

## **Insurance Companies**

The value proposition to the insurance companies will also be two-fold:

- No surgery – elimination of costly reimbursements
- Less expensive pill formulation

# PRICING

Although we recognize that E7Deg is still in its early stages of development, we believe it useful to consider a few potential pricing benchmarks in order to validate the market potential for our product. Based upon analog treatments for other viral STDs, as well as the current medical costs of treatment per infection, we believe that a pricing point of \$1,000 / person / year would be feasible.

## **Pricing based on analog treatments of other viral STDs**

We examined the drug therapy costs for several other viral-mediated STDs.<sup>5</sup> Although all these cases have a spectrum of treatments available, we still observe that the more advanced pill formulations achieve significant pricing points.

- Herpes Simplex: \$1,200 (Famciclovir – daily suppressive therapy)
- Syphilis: \$280 (Procaine penicillin plus Probenecid)
- HIV: \$2,500+ (triple therapy)

## **Pricing based on current medical costs of treatment**

Additionally we examined the average direct medical cost an HPV infection. From the CDC study<sup>3</sup>, we see that current HPV costs are estimated to be approximately \$1,200 per infected woman. A curative therapy would be expected to take place of these costs; therefore we will use \$1,200 as a ceiling on the pricing point.

Historically, treatments based on significantly novel and effective mechanisms have been granted pricing premiums over those existing on the market. As predicting these premiums in advance of actual development is difficult and subject to speculation, we take a conservative approach and include no pricing premium in our calculations.

# FINANCIALS

Ligeia's financials during the next year will be focused upon funds needed to identify lead compounds and bring E7Deg through pre-clinical trial development. Beyond this phase of development, we recognize the need for significant resources to carry through the phases of FDA approval. Therefore as mentioned previously, Ligeia will seek an experienced pharmaceutical partner to bring the drug through development and shoulder the costs of clinical trials.

## Initial funding requirements

We anticipate that our first year of operations will require \$2 million. Additional financing of \$1.5 million will be needed over the following 4 quarters. Funding for the first year of operation factors purchase of capital equipment necessary to set up a screening facility, including:

(Figures in \$'000)

Scanner – 2 channel (535nm and 635 nm):	\$60
HT-SPR Biacore for secondary assays and Kds:	\$450
Amino slides:	\$20
Reagents/Solvents:	\$80
Consumables:	\$10
Glassware and small equipment:	\$50
3 Full Time Screening Employees (@ \$60k/Yr):	\$180
<u>Laboratory Rent:</u>	<u>\$45</u>
<b>Total Costs:</b>	<b>\$895</b>

This funding will be sufficient for taking our lead compound through preclinical development.

## Anticipated future funding requirements

Ligeia anticipates the following funding needs conditional on achieving technological and developmental milestones:

Q2 2004 – Secure initial \$2 million funding

- Next milestone – Fund platform development work, initial capital expenses

Q1 2005 – Secure follow on \$1.5 million of seed funding

- Next milestone – Pre-clinical trials with animals

2 years from now – Initial partnership payment

- Next milestone – Phase I trials

3 years from now – Milestone payment from partner

- Next milestone – Phase II trials

5-7 years from now – Milestone payment from partner

- Next milestone – Phase III trials

## Exit strategy

We anticipate a large pharmaceutical company will purchase Ligeia. We believe that the combination of our novel technology platform and our future portfolio of small molecule compounds will attract interested parties, and will allow Ligeia to negotiate a favorable sales agreement.

## Income statement & statement of cash flows

At this point in time, it is unrealistic to precisely forecast Ligeia's future income and cash flows, especially beyond 5 years. Income and cash flows are highly dependent upon exact deal terms established with our development partner. Since this partnership has not yet been established, we can only suggest potential terms and streams of revenue.

## Revenue generation through development partnerships

We anticipate that the initial revenue streams for Ligeia will be generated from a development partnership with a large pharmaceutical company. As benchmarks, we have chosen to examine the following partnerships between our competitors and their co-developers: Stressgen-Roche, Medimmune-GSK and Epimmune-Genencor.

	<b>Stressgen</b>	<b>Medimmune</b>	<b>Epimmune</b>	<b>Average</b>
<b>Upfront</b>	\$1,000,000	\$15,000,000	\$4,600,000	\$6,800,000
<b>Milestone</b>	\$4,500,000	N/A	\$4,700,000	\$4,600,000
<b>R&amp;D</b>	\$21,000,000	\$11,000,000	N/A	\$16,000,000

*Table 4: Competitors have split revenues between Upfront, Milestone and R&D payments*

We have further broken-down the Stressgen-Roche partnership to reflect the annual revenues based on milestone and R&D payments. Ligeia intends to use these examples as benchmarks for future negotiations.

	<b>2002</b>	<b>2003</b>	<b>2004</b>
<b>Milestone</b>	\$1,000,000	\$4,500,000	\$0
<b>R&amp;D</b>	\$5,400,000	\$5,200,000	\$10,400,000
<b>Total</b>	\$6,400,000	\$9,700,000	\$10,400,000

*Table 5: Ligeia will use industry benchmarks in structuring our partnership arrangements.*

# RISK MANAGEMENT

The largest risk associated with Ligeia is common to all drug discovery companies. Statistically, only 1 in 5000 lead compounds make it from pre-clinical through clinical trials to be marketed as a drug. Ligeia spreads this risk in two ways:

## **Partners shoulder the risk**

First, we will not conduct costly clinical trials. We will follow the model of other small drug discovery companies and partner with a large biotech or pharmaceutical company, which is better positioned to shoulder risk. Ligeia will focus its efforts primarily upon product R&D and co-product development, and rely upon our experienced partner for clinical testing, manufacturing, sales, and distribution.

## **Ligeia's drug discovery platform is unique**

Second, the flexibility of our platform technology will allow Ligeia to build a portfolio of compounds, targeting additional viral-mediated diseases such as Hepatitis C, as well as certain types of cancers, with the same principle advantages of oral administration and high catalytic activity. Furthermore, because of the novel mechanism of action of our solution, Ligeia is positioned to go after targets that traditional drugs screens are unable to pursue.

## **Addressing Lipinski's Rule of Five**

Lipinski's Rule of Five is a set of empirical guidelines first outlined by Christopher Lipinski at Pfizer, and used by medicinal chemists to assess the "drugability" of lead compounds. Through retrospective analysis of drugs that have been brought to market, Lipinski observed that on average, the molecule mass of an aqueous and permeable drug is below 500 Daltons. Ligeia's lead candidates will most likely be on the order of 1000 Daltons by virtue of the screen and crosslinking method used to construct them.

To ensure solubility and permeability of our compounds, we have taken the following steps:

- We incorporate into our libraries data from studies of large natural drugs (>500 Da), which relates the solubility and permeability of compounds to their structural rigidity.
- We diversify the sampling of chemical space represented in our libraries. Unlike screens for small molecule inhibitors, Ligeia is not limited to libraries of compounds that bind enzyme active sites, which are typically hydrophobic pockets.
- We are exploring other vehicles that may be used in conjunction with our product to facilitate successful absorption into infected cells.

### Additional business risks

We recognize the difficulty and time needed to successfully bring a drug to market. Below we have identified additional risks to Ligeia and outline the steps the team is taking to mitigate them.

Risk	Probability of Occurrence	Impact on Ligeia's Success	Steps to Address
I.P. license is not granted	Low	High	All historical OTL licensing steps including a business plan, and the participation of the inventor, have been adhered to.
Competitors product to market first	Low	Medium	At market time, Ligeia's solution will be superior because it is cheaper and preferred by patients.  See competition and competitive advantage.
Inability to find a partner	Medium	High	Will begin discussions once initial IP is locked in
Inadequate funding to fund first two years of venture	Medium	High	Ligeia will be focusing on VC funding as well as SBIR and NIH grants using both Harvard and MIT connections.
Inadequate management team	Low	High	Beyond the 50K, Ligeia seeks an experienced life-sciences executive to take the reigns and act as CEO.

*Table 6: Ligeia's management team is positioned to competently assess and address risk*

## THE TEAM

The company has in place an outstanding team with scientific, operational and legal experience. We believe our team is well suited for management at the initial seed and early R&D funding stages. Beyond that, as Ligeia gains further exposure it will become critical to recruit an experienced life-sciences executive to take the reigns as CEO and lead us into the future.

Ligeia is also committed to putting together a dedicated Scientific Advisor Board. We are already in negotiations with various faculty members and experts in the field from M.I.T. and Harvard Medical School, who are willing to advise Ligeia, should we progress beyond the 50K.

Below are the members of the current team.

**Daniel Janse:** Daniel will receive his Ph.D. in Biological and Biomedical Sciences from Harvard University in the fall of 2004. The work described in his thesis, which forms the basis for Ligeia's technology platform has been converted into a pending patent, of which he is an author.

**David Kuo:** David is a 2<sup>nd</sup> year MBA at the MIT Sloan School of Management specializing in Financial Management and Biotechnology. His previous experience includes time in Pfizer's New Product Development / Global Market Analytics group (focusing on oncology and immunology), as well as management consulting.

**Ali Yeyinmen:** Ali is a strategy consultant, helping biotechnology start-ups and medical technology companies with market analysis and business modeling. He has more than eight years of large-scale systems and application development experience. His focus has been consistently at aligning business processes with resources and organizational goals. Ali obtained his BS in Business Administration from University of Vermont and his MBA from the MIT Sloan School of Management.

**Carl Chen:** Carl is at the MIT Sloan School of Management's mid-career Management of Technology Program. The program's focus is on "leadership and innovation" management. Carl's previous experience includes time as an executive in the technology outsourcing industry and includes stints as legal counsel and consultant for major Asian corporations and national governments. Carl also serves on the technology advisory board of a major TAIEX listed corporation.

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