Agaritine

The Potential Magic Bullet against Leukemia

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ALS 457
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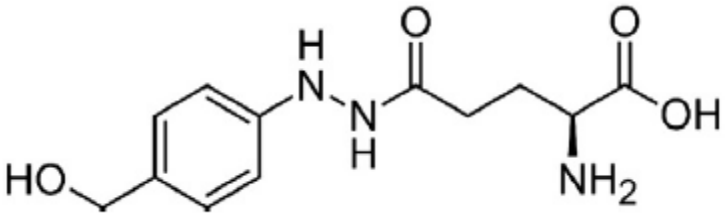


Executive Summary/Introduction

Agaritine is a chemical compound isolated from *Agaricus blazei* Murrill, a mushroom used as a traditional folk remedy in Brazil. Recently, a research team in Japan successfully demonstrated in vitro that Agaritine could selectively kill four different leukemia cell lines in a dose-dependent manner while leaving normal white blood cells unharmed. This could potentially serve as a "magic bullet" against leukemia, a deadly disease that kills nearly 22,000 people a year. Of the four major leukemia types, Acute Myeloid Leukemia (AML) only has a 23.6% overall survival rate. But the elderly AML population has the most dire need for a safe and effective chemotherapy drug, as this population only has a 2% five-year survival rate. Therefore, we aim to first address this critical unmet need in the market, which currently is about $147 million with 460,000 units sold annually. Our drug is projected to generate between $100-150 million for the AML market while pricing it modestly between $500-$750/dose, which is much lower than biologics that are dominating certain leukemia market segments. Even with the standard drug development risk, IP risk, and competitive risk from nutraceuticals, they can be addressed effectively. We hope you will invest in us to help develop this potentially powerful drug to market and help bring about a cure for leukemia.

Value Proposition

Leukemia is a form of blood cancer that affects white blood cells and its progenitors in the bone marrow. Latest available statistics from Centers for Disease Control and Prevention (CDC) show that 36,273 people were diagnosed with leukemia in 2007, killing 21,928 people in the United States[1]. Estimates from the Leukemia and Lymphoma Society reveal 44,600 new diagnoses of leukemia in 2011, and that 274,930 people in the U.S. are either living with the active form of the disease or under remission[2] (Figure 1). There are four different types of leukemia, differentiated by cellular origin and

[1] (Centers for Disease Control and Prevention, 2010)
[2] (Leukemia & Lymphoma Society, 2011)

whether it is acute or chronic (Table 1). Although survival rates for leukemia have increased the past several decades, the overall survival rate remains at 56.5%, with large disparities existing among the four types. For instance, the lowest overall 5-year survival rates is among the Acute Myeloid Leukemia (AML) population at 23.6%, whereas the other types of leukemia have at least a 55.2% survival rate (Table 2). In fact, AML is estimated to have claimed over 9,000 lives in 2011, more than the other three types combined (Table 3). Among the AML patients, survival rates differ among age groups as children and adolescents below the age of 15 have a much higher survival rate (63.6%)[3] than the elderly, who tend to acquire AML more than any other age group and have only a 2% five-year survival rate[4] (Figure 2). The reasons are that the elderly tend not to tolerate high-dose chemotherapy as well as those who are younger, and they tend to have other debilitating chronic diseases (ie, heart disease) that complicate treatment[5]. Additionally, 72% of AML patients over the age of 70 who underwent intensive chemotherapy (cytarabine) had an 8-week mortality of equal or greater than 30% and a median survival of less than 6 months[6]. Therefore, there is a significant need to have a more effective and tolerable form of chemotherapy for the elderly population with AML.

Agaricus blazei Murrill is a mushroom that has been used as a folk remedy in Brazil for various ailments, such as cancer, diabetes, and chronic hepatitis[7]. Known as mushroom of the Sun, Life and God in Brazil or "princess matsutake" in Japan, it was discovered in 1960 by Takatoshi Furumoto and brought back to Japan for cultivation and further study. Over the past decades, researchers have studied extracts of *Agaricus* in the effort to find the key chemical compounds that may be providing these medicinal effects. Agaritine is one of the compounds that has been isolated and purified from *Agaricus*, and just only recently been examined by a team of researchers in Japan. A team led by Dr. Masahiro

[3] (Leukemia & Lymphoma Society, 2011)
[4] (Menzin, Lang, Earle, Kerney, & Mallick, 2002)
[5] (Bradley, Dahman, Jin, Shickle, & Ginder, 2011)
[6] (Kantarjian, et al., 2010)
[7] (International Science and Health Foundation, 2010)

Endo discovered that Agaritine purified from *Agaricus* showed significant anti-tumor activity against leukemia cells in vitro, selectively killing four different leukemia cell lines in a dose-dependent manner while keeping healthy white blood cells unharmed (Figure 3)[8]. Agaritine was found to be non-carcinogenic, heat-stable, and water-soluble, which are desirable properties for a drug. Furthermore, Dr. Endo and his colleagues demonstrated apoptosis[9] as the mechanism for Agaritine's ability to kill one of the leukemic cell lines, U937. This discovery has the potential to be the "magic bullet" that leukemia patients, especially the elderly patients with AML, with some hope for an effective cure. Our company, QN Pharmaceuticals, is developing Agaritine in the hopes to provide such a cure to fulfill the unmet need in the leukemia market. Even though these studies are only at the in vitro/cellular level, they are very promising and we hope to further demonstrate safety and efficacy through pre-clinical animal studies followed by human clinical trials, in the hopes to gain FDA approval for market.

Pricing for our Agaritine drug is a challenge due to several factors. Current prices of chemotherapy drugs (small molecule drugs) are mostly off-patent, so the prices are generally very low. For that reason, generic drug manufacturers were not incentivized enough to produce large amounts, leading to the recent shortage of chemotherapy drugs for leukemia, especially for AML[10]. They include cytarabine and daunorubicin, two of the most important chemotherapeutic drugs against AML. Since antibody therapeutics and biologic therapeutics for leukemia are driving the market, one of the market research reports believes chemotherapy growth will be in the single digits through 2015[11]. Because we are still 12-15 years away from FDA approval, the market will most likely change from where we are today. But based on a new patented drug with a unique value proposition that treats a segment of the market with a significant unmet need, and using the current Medicare pricing for generics cytarabine

[8] (Endo, et al., 2010)
[9] Apoptosis, or programmed cell death, worked via caspase activation through cytochrome c release from the mitochondria in this case. Apoptosis is an important immunological method for killing cancer cells. (Akiyama, et al., 2011)
[10] (Link, Hagerty, & Kantarjian, 2012)
[11] (Decision Resources, 2011)

and daunorubicin as a guideline, we have come up with a pricing model between $500-$750/dose, well below the cost of a biologic drug but priced competitively enough to generate enough revenue while keeping the price affordable enough for most patients (Table 4). We have come up with this price based on our calculation of the current generic chemotherapy market, simplified by taking the top two drugs in the field (Daunorubicin and Cytarabine). By using prices provided by MediCare[12] and the dosing schedules typical for these drugs[13,14], we generated the market figure of $147.5 million with 460,000 units being sold (Table 5). We then made several assumptions regarding Agaritine and the future AML market. We conservatively assumed that there will be a modest increase of 10% demand for these drugs by the time of market release, therefore approximated the unit demand to be 500,000. We then made calculations toward price/dosage making assumptions that Agaritine would be dosed on the average of 4 days and treating 25,000 patients. Depending on the unit pricing ranging from $150-$500, revenues between $75M to $250M were observed. Considering that Daunorubicin is priced between $79-$173/dosage application and Cytarabine is priced between $1.30 to $770/dosage application, we took a conservative approach to price it well above the lower priced generics while not exceeding the $770 price for liposomal Cytarabine. Pricing adjustments will have to be made as more clinical data are acquired and comparing Agaritine's safety and efficacy profile against other competing therapeutics as we approach market release. Additionally, it is even conceivable that with the high cost of biologics that are likely to rise more in 12-15 years, we may be able to price this drug even higher depending on economic realities and market conditions at that time. But currently, $500 - $750/dose is a fair number for our pricing model.

[12] (Centers for Medicare & Medicaid Services, 2012)
[13] (Drugs.com, 2009)
[14] (Drugs.com, 2011)

Market Definition

As stated previously, the current size of the U.S. market for AML is estimated to be $147.5 million, with 460,000 units of drugs being sold (Table 5). To generate these numbers, we have made some assumptions to simplify the calculations. For instance, we have assumed that all 13,000 new cases of AML per year will undergo induction therapy[15], and that of the remaining 18,000 surviving patients, half will have induction and/or refractory therapy[16]. There are also variations in the numbers of days of treatment for induction and refractory treatments, and for simplicity, we have taken an average of the two. Additionally, we were cognizant that most patients will have a combination treatment of both drugs, therefore the numbers of patients appear higher than expected based on the prevalence figures alone. Also, we have generated the model based on equal numbers of patients taking either form of the drug, for simplicity. The market may be bigger by two or even three fold, as we did not factor in the potential for additional courses of treatment. We felt that the additional number of patients would have offset such additional courses. Therefore, we believe there is a greater potential for underestimation rather than overestimation, as we wanted to error on the side of being conservative than being overly aggressive in our calculations.

We have segmented the market to AML, as we believe this is the area of greatest need, especially for the elderly population. However, there is also the potential to treat other subsets of leukemia, such as ALL, which has a much higher prevalence near 59,000 people. In fact, an ALL cell line called MOLT4 was one of the leukemic cell lines that was effectively killed by Agaritine in Dr. Endo's in vitro study[17]. Additionally, another cell line in the study, K562, was originally from a CML patient, which opens up another market of 26,000 patients. But both ALL and CML have much higher survival rates, while the overwhlemingly poor prognosis of the elderly AML population is very dire and the FDA would

[15] Induction therapy refers to the initial course(s) of chemotherapy to try to drive the cancer into remission.
[16] Refractory therapy refers to follow-up treatments after remission, to eliminate all remaining traces of cancer and prevent the cancer from returning.
[17] (Endo, et al., 2010)

more likely to favor this market in approving Agaritine. Therefore, both from an unmet need standpoint and a regulatory standpoint, it is more strategically favorable to target the elderly AML market. Once clinical success is demonstrated in that patient population, we may branch out into other subsets of leukemia.

To market a new drug, gaining the trust and buy-in of marquee customers are very important, so that they would be the biggest advocates as we move forward into other market segments. Thus, defining the end customer as patients, the three most likely marquee customers (patients) are (1) elderly AML patients, (2) other AML patients, and (3) ALL patients (1420 deaths in 2011) (Table 3). CML and CLL patients are widely treated with biologics, such as imatinib (Gleevec)[18] and monoclonal antibody rituximab (Rituxan)[19], which are the preferred therapeutics for those particular market segments. To reach out to these patient populations, we will approach and market to non-profit organizations like Leukemia & Lymphoma Society and the American Cancer Society, as well as major leading health care institutions in the field of leukemia such as the Mayo Clinic, Johns Hopkins Kimmel Cancer Center, and MD Anderson Cancer Center at the University of Texas[20]. We will plan to engage with these top facilities as we look for collaborators for clinical trials. Once safety and efficacy are demonstrated during trials, these top hospitals will likely continue to use Agaritine to treat their patients and also inform other leukemia doctors throughout the country and beyond. This will help us gain additional market share in the future and help offer a cure to many patients in need.

Solution Feasibility

So far, we have identified the market segment, pricing strategy, and the approaches to gain entry and propagate through the market. In vitro research work has been very promising thus far, and

[18] (Okimoto & Van Etten, 2011)
[19] (Hornberger, et al., 2012)
[20] (Dulcinea Media, 2012)

we are very optimistic with Agaritine's chances to move further along in the drug development process. The fact remains, however, that drug development is a very costly and risky process, taking nearly 15 years from the point of discovery and costing well over $1 billion in developmental costs until market approval (Figure 4)[21,22]. We already have a slightly less risk than other drug development projects, because Agaritine is an isolated compound from a naturally occurring mushroom that has been used by indigenous people for many generations to treat various ailments. While it is true that such anecdotal evidence is not convincing enough for trained scientific minds to determine that Agaritine treats disease X with Y % efficacy, at least it appears that the compound is relatively safe in humans, which already provides us with a preview into Phase I trials. Additionally, *Agaricus* and Agaritine are both available as dietary herbal supplements, and are regularly consumed in Brazil and Japan, among other places in the world, with relative non-news about dangers or harm. Granted, the quality and potency may vary with such products. But this is a much better position than starting completely from scratch, such as in the standard drug discovery and development process, which is dependent on generating thousands of potential compounds to see which ones may work. At the very minimum, there is already some information from human experiences of Agaritine and *Agaricus*. But the definitive way is to generate data under strict scientific conditions, with Agaritine samples of sufficient quality and potency, and perform animal testing (toxicology, pharmacokinetics, pharmacodynamics), followed by human testing to demonstrate safety and efficacy. Therefore, this risk may be mitigated more as we proceed forward with development.

Regulatory risk may also be decreased with Orphan Drug Designation. Because the AML market segment is less than 200,000 patients, Agaritine's target market can be considered as an orphan drug. Once designated as an orphan drug, we will enjoy financial benefits and incentives that could offset

[21] (DiMasi, Hansen, & Grabowski, 2003)
[22] (Burrill & Company, 2011)

some of the developmental costs (Table 6)[23]. This is an attractive option to gain additional 7 years of market exclusivity and obtaining tax credits for the costs of clinical research, further defraying costs and enhancing revenue opportunities.

Another risk with this project would be the intellectual property (IP) issue. Upon researching the IP for Agaritine, we discovered that a patent that was filed on March 10, 1983 and assigned to the Coca-Cola Company (2-acylimidazole)[24] (Figure 5) may cover the class of compounds that Agaritine is classified with (phenylhydrazine)[25] (Figure 6). The chemical structures are a bit similar, but not exactly alike. While the patent may not cover Agaritine, we will need to seek consult with a patent attorney as well as an organic chemist to determine whether Agaritine falls under the Coca-Cola IP. Additionally, the Coca-Cola patent specifically cites and provides data for its own compounds' ability to "decrease in vivo leukocyte populations and are consequently useful as immunosuppressive medicinal agents for prevention of transplanted tissue rejection, treatment of leukemia and treatment of cell-mediated autoimmune disease."[26] A pharmaceutical company in Texas, called Lexicon Pharmaceuticals, has filed a series of patents for the treatment of autoimmune and inflammatory diseases, but their base chemical compound is even more distant than Agaritine, so it is doubtful that their compounds would present an issue (Figure 7)[27] (Figure 8)[28]. Again, we will need to consult with patent professionals to ascertain that we have the freedom to operate in this space. If not, we will seek licensing arrangements with the relevant parties to prevent potential patent infringement(s) and gain the freedom of operation.

Once we have gained entry, we will patent the process of producing Agaritine chemically as well as attempt to patent the composition itself. Since the leukemia market is small compared to other

[23] (U.S. Food and Drug Administration, 2009)
[24] (Kroeplien & Rosdorfer, 1983)
[25] (Endo, et al., 2010)
[26] (Kroeplien & Rosdorfer, 1983)
[27] (Augeri, Bagdanoff, Baugh, Carson, Jessop, & Tarver, 2008)
[28] (Augeri, Bagdanoff, Boteju, Carson, Jessop, & Kimball, 2007)

major diseases, we do not anticipate other entrants from the pharmaceutical industry into this market. We perceive the largest threat to be the nutraceutical supplement industry, which will continue to produce and sell *Agaricus* to the general public. However, we will differentiate ourselves by emphasizing the quality and potency we offer as a pharmaceutical product, and the confidence of safety and efficacy that our clinical trial data will provide. Additionally, we plan to offer this drug in multiple forms, not only in oral form, but in intravenous form that's highly desirable for chemotherapy purposes, which nutraceutical companies cannot offer. Since AML is a deadly disease, cancer patients can ill afford to take nutraceutical from of Agaritine of questionable quality and potency and risk their own lives. Therefore, we are confident that leukemia patients, especially with AML, will seek our drug rather than the nutraceutical form.

As we identified, the largest risks are drug development risk, IP, and threat from nutraceuticals. We have addressed each of these risks. To reduce cost and time for development, we may be able to leverage relationships with research groups and health care facilities in Brazil and Japan, who are more knowledgeable and have the background in dealing with *Agaricus* compounds. Recruiting patients for clinical trials may be slightly easier than the U.S. since these patients have had exposure to *Agaricus* or Agaritine and may be more willing to undergo clinical trials with a mushroom-based drug compound. Therefore, one approach is to try to gain regulatory approval in Brazil and/or Japan first, before attempting to do the same here in the United States.

Conclusion

Agaritine offers a unique value proposition in treating leukemia. In vitro data have been very convincing in its potency to kill leukemia cells, while keeping normal white blood cells unharmed. More recently, its mechanism has been elucidated to be apoptosis, further demonstrating efficacy. For market entry, we have identified elderly population with AML to be the market segment with the most

need. With a $148 million market for the top 2 generic chemotherapy drugs for AML, we anticipate to generate between $100-150 million by market approval in 2024-2027, assuming that Agaritine will have overwhelming market penetration in the AML segment. At a modest price of $500-$750/dose, we will price it well below the cost of biologics, so we anticipate great demand for Agaritine. Even though drug development risks, IP risk, and threats from nutraceuticals may still exist, they can be mitigated to a certain extent. We hope that you will consider investing with us to further develop Agaritine and help bring about a cure for this deadly disease.

Appendix

Figures

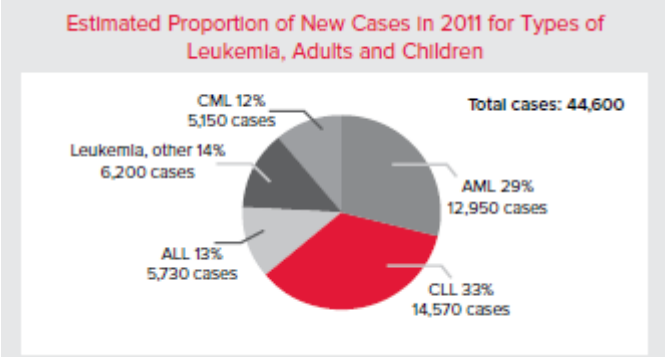


Figure 1: Estimated New Cases of Leukemia by Type (2011) (Source: Leukemia & Lymphoma Society)

Figure 2: The elderly are especially susceptible to acquiring AML. (Source: Leukemia & Lymphoma Society)

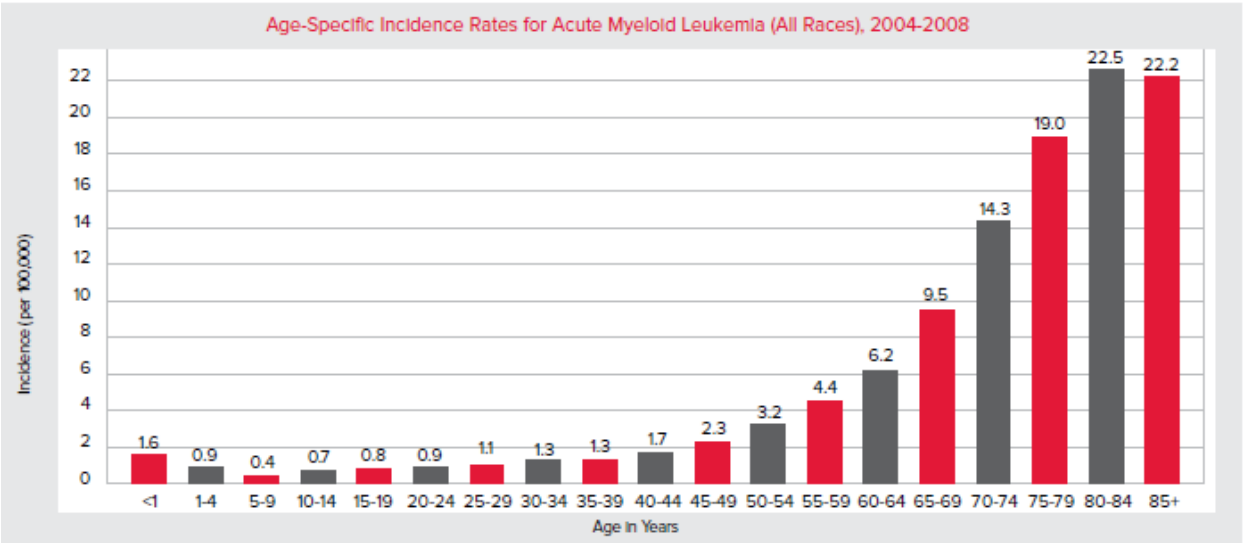
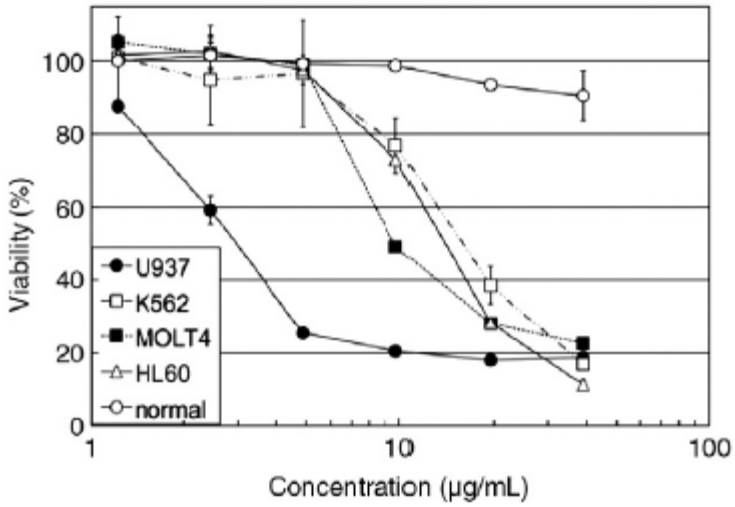


Figure 3: Agartine selectively killed four different leukemia cell lines in a dose-dependent manner while keeping normal white blood cells unharmed. (Endo et al, 2010)



Anti-tumor activity of agaritine against leukemic cells. Leukemic cells (U937, K562, HL60 and MOLT4) and normal lymphocytes were incubated with 0 to 40 μg/mL of agaritine for 48 h. Cell viability was assessed by using Cell Counting Kit-8. Agaritine showed a suppressive effect on all the leukemic cell lines examined, with IC_{50} values of 2.7, 9.4, 13.0, and 16.0 μg/mL for U937, MOLT4, HL60 and K562, respectively, but showed no significant effect on the normal lymphatic cells at concentrations up to 40 μg/mL. Data represent means of three experiments with SD.

Figure 4: Drug development is a costly and risky process. (Source: Burrill & Company, 2011)

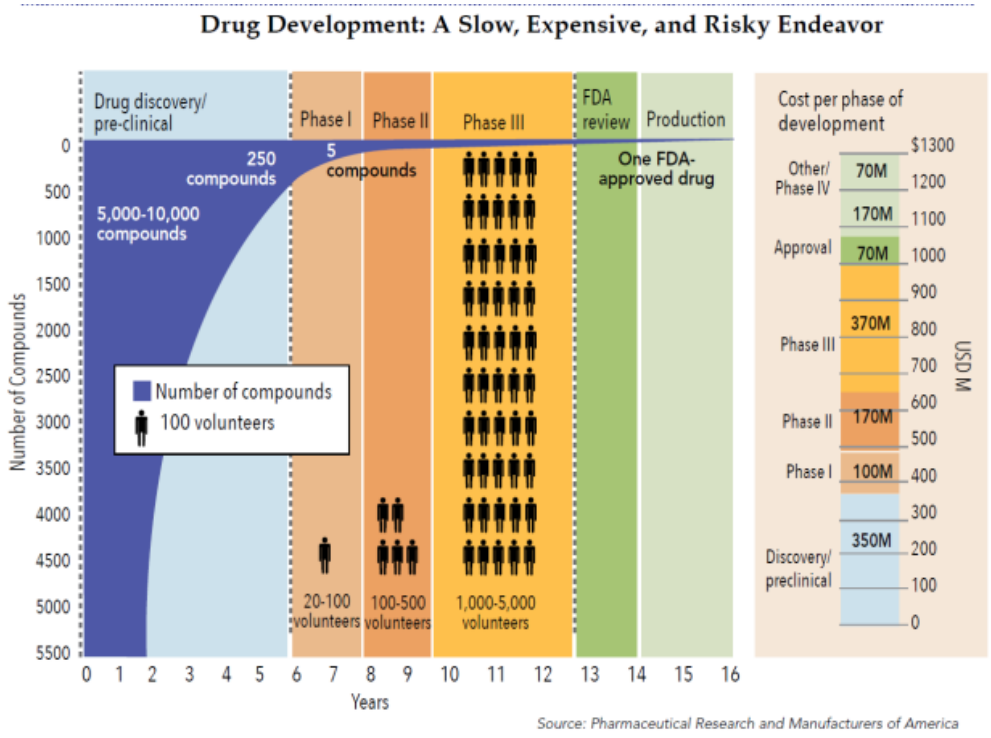


Figure 5: 2-acylimidazole compound and its derivatives claimed by Coca-Cola (US Patent 4,567,194)

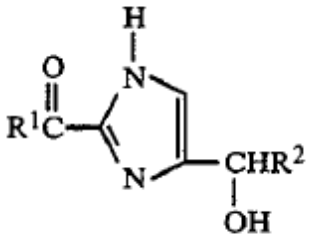
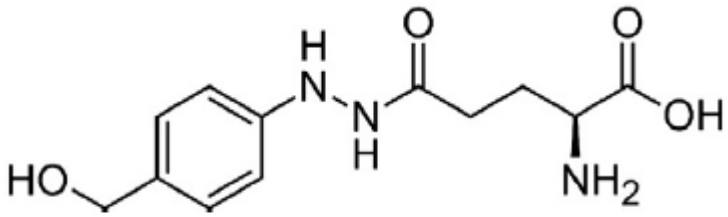


Figure 6: Structure of Agaritine (Akiyama et al, 2011)



Structure of agaritine

Figure 7: Structure of the heterocyclic base compound as published on Lexicon Pharmaceutical's patent (US 2009/0030050)

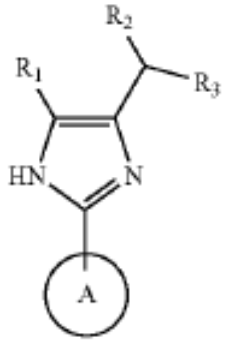
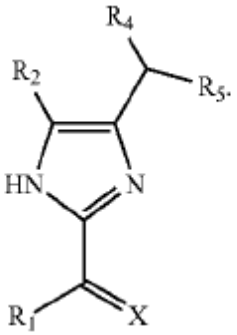


Figure 8: Structure of the imidazole-based compounds as claimed by Lexicon Pharmaceuticals (US 7,649,098)



Tables

Table 1: AML ranks third in prevalence among the four major types. (Source: Leukemia & Lymphoma Society)

Approximate U.S. Prevalence of 4 Major Types of Leukemia (2008)	
Type	Prevalence
Acute Lymphoblastic Leukemia (ALL)	58,854
Chronic Lymphocytic Leukemia (CLL)	105,119
Acute Myeloid Leukemia (AML)	30,993
Chronic Myeloid Leukemia (CML)	26,359
Total	221,325

Table 2: Survival rate is significantly lower for AML patients. (Source: Leukemia & Lymphoma Society)

Five-Year Relative Overall Survival Rates by Leukemia Type (2001-2007)	
Type	Survival Rate
Acute Lymphoblastic Leukemia (ALL)	66.6%
Chronic Lymphocytic Leukemia (CLL)	80.8%
Acute Myeloid Leukemia (AML)	23.6%
Chronic Myeloid Leukemia (CML)	55.2%
Overall	56.5%

Table 3: AML claimed more lives in 2011 than the other three types combined. (Source: Leukemia & Lymphoma Society)

Estimated Deaths by Leukemia Type (2011)	
Type	Deaths
Acute Myeloid Leukemia (AML)	9,050
Chronic Lymphocytic Leukemia (CLL)	4,380
Acute Lymphoblastic Leukemia (ALL)	1,420
Chronic Myeloid Leukemia (CML)	270
Other (unclassified)	6,660
Total	21,780

Table 4: Agaritine drug pricing will most likely be between $500 to $750/dose, well below the cost of biologics but competitively priced for a novel small molecule drug.

Agaritine Revenue Model for AML						
Units	Unit Price ($)	Revenue ($)	Dosing Schedule (Days)	Body Surface Area[29] (m^2)	Patients	Price/Dose ($)
500,000	150	75,000,000	4	2	25,000	375
500,000	200	100,000,000	4	2	25,000	500
500,000	300	150,000,000	4	2	25,000	750
500,000	400	200,000,000	4	2	25,000	1000
500,000	500	250,000,000	4	2	25,000	1250

[29] (GlobalRPh.com, 2012): Body surface area was calculated to be $2m^2$, based on the average size of an American at a height of 69 inches and 190 pounds (Ogden, Fryar, Carroll, & Flegal, 2004).

Table 5: Current market share for AML, based on top 2 generic drugs in the market

Existing Market Share Calculation								
Drug	Medicare Cost/Unit	Treatment Regimen	Patients	Body Surface Area [30] (m^2)	Dosing Schedule (Days)	Dosage Pricing ($)	Market Share ($)	Units
Daunorubicin HCl	10mg injection: $17.638	INDUCTION: 45mg/m^2/day IV on days 1,2, and 3; REFRACTORY: 2 days	11,500	2	2.5	79.371	4,563,833	57,500
Daunorubicin HCl citrate (liposomal)	10mg injection: $57.664	INDUCTION: >age60 : 30mg/m^2 IV days 1,2,3 for course 1; days 1 & 2 on subsequent course in combo with Cytarabine (100mg/m^2 IV daily days 1-7 first course, 5 days for subsequent course	11,500	2	2.5	172.992	9,947,040	57,500
Cytarabine	100mg injection: $0.867	INDUCTION THERAPY OF AML: 100mg/m^2/day to 200mg/m^2/day by continuous IV infusion 5-10 days, repeatable every 2 weeks. REFRACTORY: 2-3g/m^2 IV every 12 hr up to 12 doses	11,500	2	7.5	1.3005	224,336	172,500
Cytarabine (liposomal)	10mg injection: $513.167	Same as above	11,500	2	7.5	769.7505	132,781,961	172,500
Totals							147,517,170	460,000

Table 6: Benefits of Orphan Drug Designation (FDA)

Benefits of Orphan Drug Designation
Annual grant funding to defray the cost of clinical testing
Tax credits for the costs of clinical research
Assistance in clinical research study designs
Seven-year period of exclusive marketing after an orphan drug is approved
Waiver of Prescription Drug User Fee Act (PDUFA) filing fees (over $1 million/application for FY 2009)

[30] (GlobalRPh.com, 2012): Body surface area was calculated to be 2m^2, based on the average size of an American at a height of 69 inches and 190 pounds (Ogden, Fryar, Carroll, & Flegal, 2004).

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