

Antibe Therapeutics: The Next Generation of NSAIDs

Executive Summary

Non-Steroid Anti-Inflammatory Drugs (NSAIDs) are some of the most commonly prescribed drugs in the world. Despite their popularity, these drugs come with a number of serious side effects. Every year in the US, approximately 100,000 people are hospitalized and more than 16,000 die due to the gastrointestinal (GI) side effects of NSAIDs alone. In the elderly, the cost associated with GI related toxicity associated from NSAIDs exceeds $4B annually. We believe Antibe Therapeutics (ATBPF, ATE.V) has found a solution to this problem. By attaching a Hydrogen Sulfide (H\textsubscript{2}S) releasing moiety to Naproxen, Antibe was able to create an NSAID, ATB-346, that not only possesses a drastically reduced GI toxicity profile, but is also more effective at relieving pain and inflammation than other NSAIDs. While the potency of ATB-346 has yet to be proved, it will be soon. Antibe has just completed dosing its phase 2b efficacy study for patients with osteoarthritis. Data from this important study is due by the end of April. This report consists of two parts: the data Antibe has generated thus far which support our claim that the company has developed a safe and effective NSAID and our scientific research that supports the company’s data.

Table of Contents

Introduction 1
Can H\textsubscript{2}S Counteract the Toxicity of COX-1 Inhibition? 7
Understanding H\textsubscript{2}S 9
Redox Signaling 11
The Therapeutic Potential of H\textsubscript{2}S 13
The Many Side Effects of NSAIDs 15
Using H\textsubscript{2}S to Mitigate the Side Effects of NSAIDs 20
Conclusion 23
INTRODUCTION

“All things are poison, and nothing is without poison, the dosage alone makes it so a thing is not a poison.” ~ Paracelsus

Historically, hydrogen sulfide (H₂S) was known as a toxic gas characterized by the strong odor of rotten eggs. Until the 1990s, the research on H₂S was mainly focused on its toxicity. Accidents in industrial settings showed the danger of the gas, as exposure to high concentrations of H₂S caused collapse, unconsciousness and respiratory paralysis, and ultimately death. Since then, new knowledge has positively transformed the way H₂S is perceived. Studies have uncovered many physiological functions of H₂S in biological systems including the endogenous production of H₂S in many parts of the mammalian body.

Figure 1: Source – Antibe Investor Presentation

The importance of H₂S in life cannot be overstated. The roots of H₂S in life have been found to be deep – going back to the very origin of life itself. This small simple molecule holds great regulatory power over life’s functioning. There is no cell, no tissue, no organ that is not affected by H₂S in one way or another. The harnessing of H₂S therefore holds immense therapeutic potential in treating any number of different diseases. Towards this end, Antibe Therapeutics (Antibe), a public biotech company is working on a platform that attaches an H₂S donating molecule to existing NSAIDs.

NSAIDs are a class of drugs that provide analgesic (pain-reducing) and antipyretic (fever reducing) effects. The NSAID class of drugs includes prescription and over-the-counter (“OTC”) brands such as
naproxen (Aleve), celecoxib (Celebrex), ibuprofen (Advil), and Aspirin. Unfortunately, NSAIDs have a wide range of side effects that have been well documented over the decades they’ve been in use.

These often-prescribed drugs account for tens of thousands of deaths every year and many more hospital visits:

“Some estimates suggest that each year more than 100,000 patients are hospitalized for NSAID-related GI complications alone, with direct costs ranging from $1800 to $8500 per patient per hospitalization. Moreover, it has been reported that 16,500 persons die annually from these complications. In the elderly, the medical costs of adverse GI events associated with NSAID use likely exceed $4 billion per year.”

Figure 2: Source – Tulane University

Now what if I told you there was a drug that not only was more efficacious at alleviating pain and inflammation than the currently available NSAIDs, but also had none of the toxic side effects. To quote Bob Ryan of Entourage fame, “Would that be something you’d be interested in?”.
The market certainly thinks so. Demand for NSAIDs with better GI safety is so high that Celebrex and Vioxx grossed over $1B in sales in their first year alone. For perspective, Antibe’s current market cap is less than $100mm USD.

Unfortunately, as is too often the case when something is too good to be true, it usually is. As selective COX-2 inhibitors, the drugs were fundamentally flawed. Vioxx was pulled from the market and Celebrex was eventually slapped with a black box warning once cardiovascular toxicity issues appeared. The drug makers thought they could get away with removing the COX-1 inhibition that causes much of the GI
related side effects without any repercussions. COX-1 and COX-2 play very important counterbalancing roles in the cardiovascular system.

![Image of COX-1 and COX-2 roles](image)

**Figure 5:** source

COX-1 inhibition is particularly useful for treating stroke and cardiovascular disease, which is the basis for aspirin’s use in these diseases. Allowing COX-1 to go unchecked while COX-2 is inhibited leads to a constriction of the arteries, an increase in blood pressure and potentially if the dosing is high enough a reduction in blood flow that could cause stroke.

![Image of Selective COX-2 Inhibition & Enhanced CV Risk](image)

**Figure 6:** Source – Tulane University

We are thus left with a tough choice. We can either find a way to overcome / negate the toxic side effects that come from COX-1 inhibition, or we can find a way to keep the arteries dilated without COX-
2. For its platform and lead drug ATB-346 (shown below), Antibe chose the former, pairing H₂S with Naproxen, one of the few NSAIDs that does not pose significant cardiovascular risks.

![Chemical Structure of ATB-346](image)

**Figure 7: Source – Antibe Investor Presentation**

Naproxen is well known for its toxicity issues that come from both COX-1 and COX-2 inhibition. Which leaves us with an important question:

**Can H₂S counteract The Side Effects of COX-1 inhibition?**

The answer appears to be a resounding **YES**.

In a recent phase 2b efficacy trial, 250mg ATB-346 QD outperformed 250mg Naproxen BID on a number of GI related safety metrics. At the end of the 2-week treatment period, subjects on ATB-346 exhibited an ulceration rate of 2.5%, versus an ulceration rate of 42.1% for subjects on naproxen, with a very high degree of statistical significance (p<0.001). Impressively, there was zero incidence of large GI ulcers for the ATB-346 group vs. 23.8% for the naproxen group.

![Graph showing ulceration rates](image)

**Figure 8: Source – Antibe Investor Presentation**

With a reduction in gastrointestinal damage came a number of other benefits. ATB-346 had significantly lower instances of Abdominal pain/distension, gastro-esophageal reflux disease, and nausea.
But there’s a catch...

The dosage of ATB-346 contains considerably less naproxen. 250mg ATB-346 has just 1/3rd the dosage of naproxen (250mg). Given that ATB-346 was dosed once a day vs. naproxen’s twice a day, 250mg of ATB-346 administers just 1/6th the amount of 500mg of naproxen did in the phase 2b safety trial. Thus, it’s not entirely surprising that QD 250mg of ATB-346 would be safer than BID 250mg of naproxen. It would however, be surprising (and a significant medical breakthrough) if ATB-346 could deliver a similar level of reduction in pain and inflammation as naproxen at just 1/6th the dose...

In the very same phase 2b safety trial, 250mg of ATB-346 was able to achieve the same level of COX-1 inhibition as the 500mg of naproxen, despite containing 1/6th the naproxen. Given that COX-1 inhibition is the primary driver of GI toxicity of NSAIDs, this data is nothing short of stunning, because as we saw earlier, ATB-346 is orders of magnitude more safe of the GI than naproxen.
This data is incredibly significant for two reasons. First, and most importantly, COX-1 inhibition is the primary driver of NSAID related GI toxicity. But as we saw previously, ATB-346 has little to no GI related toxicity. This clearly shows that the H₂S is having a strong impact. Which shouldn’t be entirely surprising as COX inhibition has been shown to suppress endogenous H₂S production.

“Thus, suppression of mucosal H₂S synthesis may represent another mechanism, aside from suppression of COX activity, through which NSAIDs produce GI damage.

Secondly, COX-1 inhibition along with COX-2 inhibition is the primary MoA for NSAIDs like naproxen, suggesting that ATB-346 may have similar efficacy to naproxen. In fact, there’s already evidence to support this is the case. In an earlier open-label, phase 2a study involving just 12 patients, 250mg of ATB-346 was shown to be more effective at relieving pain than naproxen.

![Image](Figure 11: Source – Antibe Investor Presentation)

It is worth noting that these patients were suffering from higher levels of pain and inflammation than the average osteoarthritis patient as shown in their DPDA* and WOMAC stiffness scores. Statistically significant improvements were also seen in both metrics. When added up, patients saw a reduction of over 40 points in their WOMAC scores in just 10 days.
Note that not only did ATB-346 lead to a level of pain reduction beyond what is historically seen in NSAIDs but that pain reduction improved as time went on suggesting ATB-346 and its H₂S molecule may be impacting inflammation on a more fundamental level. This was, for the company, an unexpected result at the time. While the company’s original goal was to improve the safety of NSAIDs it appears that they have stumbled upon a way to also reduce pain and inflammation in the body that is entirely unique and separate from the MoA of NSAIDs.

For example, a recently published mouse study showed that the pain-relieving potency of ATB-352 compared to ketoprofen was greater than 3-fold and that this enhanced potency is related to significantly elevated levels of naturally occurring endocannabinoids in comparison to the levels of endocannabinoids observed in mice treated with ketoprofen. The data makes it quite clear that H₂S holds the potential to reduce pain and inflammation above and beyond what is offered by NSAIDs. What those benefits are and how they arise will be explored in the rest of this report.

H₂S’s role in mammals let alone humans is not well studied. While the data the company has already generated clearly is strong enough in its own right to support a bet on Antibe, we feel the need to dig deeper and illuminate what we believe to be the science behind these powerful clinical trial results. In order to do this, we are going to embark on a journey that is partly theoretical and may at times extend beyond the bounds of mainstream thinking. But first we must go back to the beginning – and by beginning we mean the beginning of life on Earth.
Understanding Hydrogen Sulfide

“Nothing in Biology Makes Sense Except in the Light of Evolution”—Theodosius Dobzhansky

There can be few elements with a biochemistry as coherent as that of sulfur. This important element is crucial to myriad aspects of metabolism, catalysis, and structure. The plurality of functions in which sulfur is involved derives squarely from the numerous oxidation states in which it may exist (-2 to +6), some having great stability, some being capable of ready redox interconversions, and yet others having great instability. From the beginning, sulfur has been inexorably entwined with the evolution of organisms.

In the beginning, there was little to no oxygen (O$_2$). Energy in the form of reducing equivalents flowed outward across the Earth’s crust through ‘‘pores,’’ hydrothermal vents, and volcanoes. Much of this was sulfide, which was then oxidized in the mildly oxidizing atmosphere.

In fact, sulfide is also known as the ‘sunlight of the deep ocean’, as in this dark environment the sulfide released from the deep-sea vents is a vital source of metabolic energy for the primary producers of living matter.

There are many sulfa-oxidant bacteria in this environment that derive their metabolic energy from driving electrons from sulfide to oxygen. Moreover, multicellular organisms (e.g. tubeworms) living in the specialized environment of these deep-sea vents are also known to utilize H$_2$S as a primary source of energy, using a complex system where the worm takes up HS$^-$ from its environment, and, in turn, delivers sulfide to its internal bacterial symbionts that utilize it. According to one evolutionary theory, life, in fact, evolved near the deep-sea vents billions of years ago, prior the existence of oxygen on the planet. Therefore, primordial versions of sulfide-based metabolism may have preceded the current, oxygen-based life on the planet by several billions of years.

Once H$_2$S dependent life evolved, for the next 3 billion years, organisms continued to evolve and develop more sophisticated methods to control this energy. During this period, rain leached sulfur from the land and as it flowed into the oceans the sulfur became reduced, creating a euxinic environment that was both sulfidic and hypoxic.

The ability to cycle sulfur between reduced and oxidized states may have been key in the great endosymbiotic event that incorporated a sulfide oxidizing a-proto-bacteria into a host sulfide-reducing Archaea, resulting in the eukaryotic cell. It is theorized that eukaryotic cells arose in this environment from the combination of a sulfide-reducing Archaea and a sulfide-oxidizing a proto-bacterium. This union arguably enabled sulfur cycling and energy transfer between the cytoplasm and mitochondrion.
An alternative theory is the hydrogen hypothesis which while not as dependent on H₂S still inevitably involves the merger of two organisms which were highly dependent on sulfur-based metabolism.

For 500 million years, eukaryotic cells continued to develop and thrive in this environment as evidenced by the fact that the oldest known microfossil was a sulfide-oxidizing organism. As photosynthesis began to create O₂-rich areas “oases” in the seas, organisms living in or around these environments now had to develop strategies to detoxify this unusually reactive gas.

It was also soon realized that O₂’s reactivity could be harnessed, and this culminated with O₂ as the ultimate electron acceptor in the electron transport chain. While the increase in ambient O₂ promoted oxidative metabolism, it presented another problem: reduced sulfide disappeared. Organisms were now obligated to change to carbon-based substrates as an energy source.

Periodically in Earth’s history a variety of factors, especially global warming and increased volcanic activity, upset the oxic/sulfidic balance, and consequently the euxinic zone increased to the point where there was not much oxygen in the oceans, and H₂S was expelled into the atmosphere. This resulted in mass extinctions. The most dramatic of these was circa 250 million years ago when 97% of the animals in the ocean and 70% of those on land were killed. This stresses two important points:

1. oxygen and sulfide do not co-exist, either in the environment or in cells, and
2. animals that survived these catastrophic events had intrinsic mechanisms to cope with both hypoxia and sulfide.
These events then ensured the survival of organisms whose genome had not only retained, but also passed on the capacity for sulfide metabolism and sulfur based signaling. And the key to sulfur and sulfide signaling is redox signaling.

**Redox Signaling**

Many redox signaling mechanisms and antioxidant systems present in modern-day organisms can be traced back nearly 4 billion years to the appearance, in an anoxic environment, of the last universal common ancestor. ROS would have been scarce during this period and most likely for the ensuing 3.2-3.4 billion years of evolution because the oceans remained anoxic or severely hypoxic and became more sulfidic until the dramatic oxygenation 600 million years ago. Redox stress and signaling was not a response to ROS, but was necessitated by another stressor, reactive sulfide species (RSS). RSS were not only inextricably tied to the origin of life, but it is becoming increasingly apparent that they have persisted up to the present day as integral components of homeostasis.

Indeed, it is considered likely that the interaction of RSS with Reactive Nitrogen Species (RNS) to form S/N-hybrid species participated in forming the building blocks of life and preceded the advent of aerobic respiration and ROS formation. In this model, as the level of atmospheric oxygen rose, enabling the development of larger and more energy-efficient organisms, the ancient mechanisms of sulfur metabolism had to face the new challenge of dealing with rapid oxidation processes superimposed onto those that controlled electron transfer in all life forms until then.

This model helps to explain why many regulatory pathways are connected to fundamental sulfur-mediated electron transfer processes. As the levels of complexity increased from unicellular to larger multicellular organisms, the fundamental principles of regulation were conserved. The chemical biology of RSS, and their interaction with RNS and later on with ROS governed the emergence and evolution of Life.

To cope with reactive species cells had to develop detoxifying systems early on. Interestingly, the detoxifying systems are also based on sulfur-containing elements (i.e. thiols). The dynamic and rapid equilibria among RSS and detoxifying systems have probably been one of the most powerful driving forces connecting cellular metabolic capacity with the extracellular milieu, allowing cells to find multiple ways to survive and increase their robustness; this may have included adaptation to changes in the environment and communication to other cells, driving the emergence of symbiotic niches and the development of multicellular organisms.

The rich chemistry of the Reactive Species Interactome (RSI) offers a unique opportunity to fine-tune biological reactions, taking advantage of the diverse chemical nature and lifetimes of the intermediary products formed.

A corollary of the RSI concept is that reactive species can no longer be regarded as mere stressors. Rather, they should be considered controlled reaction products, which serve to sense and transduce information about any changes of internal and/or external conditions; as such, they may be considered as elements of a regulatory system (the RSI) that enable an integrated response to various forms of stress, for example, changes in metabolic, nutritional, and redox status, and environmental conditions.
The RSI is a tightly intertwined redox network that enables rapid sensing and adaptation of the internal cellular milieu to a changing environment. Individual cells within a given tissue/organ need to sense their microenvironment in relation to that of the entire organism to achieve a metabolic status that adequately enables the needs of their preferred activity. Similarly, the cells need to relate their individual redox status within a composite redox state that matches with other cells and organs. This necessitates reciprocal sensing of intra- and extracellular redox poise. This has to embrace cell membrane behavior and an inter-organ communication system that connects the various contributing elements and provides a readout of the global redox poise. The entirety of protein thiols serves as an important redox buffer and that extracellular thiol status helps to mark the global redox state in health and disease.

The development of this RSI based intercellular communication and the emergence of symbiotic arrangements provided new “collaborative” opportunities to cope with environmental and infectious threats as well as nutritional shortages. Longer-lived RSI metabolites may later have participated in cell-cell communication and enabled co-metabolic negotiations. As levels of regulatory complexity within those multicellular life forms increased, so did the need for communication. Yet, without appropriate protection these symbiotic life forms were still vulnerable to threats and dependent on opportunities provided by their local environment. Gaining independence and resilience against external stressors required formation of cell assemblies allowing robust growth and movement.

This may have been a driver for the development of larger multicellular organisms with distributed critical functions and enhanced resilience. **With redox processes at the heart of global regulation, all organisms larger than perhaps a few hundred cells would require an internal system to communicate metabolic activity status and perceived threat level throughout the entire system, allowing bioenergetic prioritization to survive and reproduce or in other words, an inter-organ communication system.**

![Figure 14: Source - Discoveries of hydrogen sulfide as a novel cardiovascular therapeutic.](image)
Essentially every organ system, and function, appears to be affected by exogenous sulfide and/or manipulation of endogenous sulfide production and numerous reviews tout the ubiquity of this signaling system and the potential for clinical application. Given the ubiquity of H$_2$S throughout the body, potential for H$_2$S is as remarkable as it has been overlooked.

**The Therapeutic Potential of H$_2$S**

The potential for H$_2$S for clinical application is explicit in the requirements of H$_2$S signaling for the beneficial effects for virtually all anti-aging therapies. It has been shown that regardless of what the upstream pathways are (Insulin/IGF, mTOR, AMPK, SIRT, Klotho, Nrf2, p66, GSK-3beta, etc.), there is one final common pathway for the “longevity component” of calorie restriction and other anti-aging therapies and that is the synthesis of H$_2$S by the Transulfuration pathway.

The importance of H$_2$S in anti-aging therapies is due to the primacy of reactive sulfur species in the redox metabolic pathways of life. As stated above, all redox signaling since the dawn of life has been dependent on reactive sulfur species and today despite the importance of oxygen all life still utilizes the ancient sulfur signaling pathways. All redox-dependent adaptive and hormetic responses therefore involves reactive sulfur species; and, it is through hormesis or adaptive homeostasis that we maintain our health and fight the inevitable decline in function that occurs as we age.

In his masterpiece “The Twilight of the Idols”, the German philosopher Friedrich Nietzsche stated: “What does not kill me, makes me stronger”. Indeed, at least in specific cases, exposure to low amounts of a toxic substance or stressor may render an organism more resistant to higher (and otherwise detrimental) doses of the same trigger. This adaptive response is known as hormesis (from the Greek “to set in motion”): the exposure to mild levels of harmful factors preconditions a cell or an organism in that it stimulates the activation of stress resistance mechanisms, thus fostering the cellular capacity of maintenance and repair. In other words, hormesis governs a pleiotropic pro-survival program.

As noted above, H$_2$S used to be seen only as a toxic compound. As an RSS, H$_2$S (and its companions), is potentially damaging but this also makes it an important regulator of the hormetic response. The right amount of H$_2$S can cause the body to essentially evolve into a more robust state that has a higher functionality and is less fragile to perturbations such those brought about by the reactive sulfur species that initiated the initial hormetic response.

The relevance of hormesis for both human pathophysiology and specific disease treatment is being increasingly recognized. Many if not all anti-aging interventions follow hormetric features. This is important not just because aging in general is something we should strive to fight but because all non-acute, non-infectious diseases are aging-related diseases and are amenable to treatment via the proper use of hormesis. It is through hormesis that you treat and cure chronic diseases and H$_2$S is at the core of the hormetic response.

However, it isn’t only via hormesis that H$_2$S possesses disease modifying properties. As shown previously, H$_2$S is also inextricably linked to redox potential – and thus inflammation. What the vast majority of people typically think of as inflammation is simply the signaling cascade that comes about from an excess of positive charge (a relative increase in the ratio of protons to electrons). Inflammation is essentially another way of saying low pH and low redox potential.
As a key component of redox metabolism, H₂S and its metabolites directly regulate redox potential as well as indirectly via modulation of protein functionality. In this manner, H₂S plays many important roles in regulating not only inflammation itself but also inflammatory signaling as well. In fact, H₂S has been shown to be an important endogenous factor promoting the resolution of inflammation and the repair of injury.

Inflammatory reactions are driven largely by soluble, pro-inflammatory mediators, such as leukotrienes, histamine, bradykinin, platelet-activating factor, and interleukin (IL)-1, to name just a few. Counteracting the effects of these pro-inflammatory mediators are a variety of soluble mediators that down-regulate inflammation, including lipoxins, certain prostaglandins, annexin-1 (AnxA-1), and IL-10.

"An over-production of pro-inflammatory mediators or an under-production of anti-inflammatory mediators can lead to progression from acute to chronic inflammation. Resolution of inflammation occurs through removal of the triggers of the inflammatory response (e.g., a foreign body or organism), inhibition of the recruitment of neutrophils to the site of injury, and induction of apoptosis of the infiltrated neutrophils and their subsequent clearance by macrophages. Crucial to this process is the phenotype shift that macrophages and other immune cells undergo from pro-inflammatory or anti-inflammatory." (Our emphasis in bold)

H₂S acts to induce resolution of inflammation by acting on many aspects of this process of inflammatory signaling. Importantly, it does so in a holistic manner. H₂S essentially helps to balance the inflammatory mediators in a way that, as we shall see later, is beyond the ability of standard NSAIDs.

Figure 15: Source – Hydrogen Sulfide: An Endogenous Mediator of Resolution of Inflammation and Injury

H₂S is a critical regulator of oxygen homeostasis. There is an inverse relationship between oxygen availability and tissue sulfide concentration that has been proposed to be the mechanism through which
oxygen-sensing cells, such as blood vessels and chemoreceptors detect oxygen levels and initiate appropriate physiological responses, i.e., the oxygen-dependent metabolism of sulfide is the enigmatic oxygen “sensor”.

The relationship between sulfide and \( \text{O}_2 \) at the cellular level is reminiscent of the geochemical relationship between these two gases during the evolution of the eukaryotes in that there is a reciprocal ebb and flow driven by the production or consumption of the respective gases – albeit with the ironic twist that the molecule that was once used as the primary energy source is now the reporter for the molecule that replaced it.

In other words, when oxygen is low, \( \text{H}_2\text{S} \) is elevated, and this elevated level of \( \text{H}_2\text{S} \) signals to the body that oxygen is low and the body takes appropriate action to remedy this situation. For example, \( \text{H}_2\text{S} \) signals the body to dilate the blood vessels which allows for increased oxygen flow to cells and tissues.

**\( \text{H}_2\text{S} \) can act to regulate mitochondrial functioning.** Depending on the context \( \text{H}_2\text{S} \) can be an electron donor or a terminal electron acceptor and thereby enhance mitochondrial metabolism or \( \text{H}_2\text{S} \) can act to inhibit mitochondrial metabolism. Furthermore, \( \text{H}_2\text{S} \) as a signifier of low oxygen content thereby signals stress and induces the mitochondria to adapt in a hormetic fashion.

Finally, \( \text{H}_2\text{S} \) is part of the sulfur cycle which is an important component of the symbiotic relationship we have with our microbiome. Thus, \( \text{H}_2\text{S} \) can be seen to regulate our microbiome, and vice versa.

All of these aspects of \( \text{H}_2\text{S} \) play into its immense potential therapeutic value. This value lies not just in the beneficial effects \( \text{H}_2\text{S} \) has on its own, but in combination with other drugs (ie. NSAIDs) as well.

Most drugs are made according to a reductionist approach – they don’t act holistically but rather in a very narrow and specific manner. This is one of the great missteps in modern medicine. The very nature of life and of homeostasis is the dynamic orchestration of a vast number of biological activities. Nothing happens in isolation. All biological activities affect all other biological activities.

**In attempting to affect a specific protein or pathway modern drugs cause unforeseen knock-on effects as the whole network adapts around the changes made by the drug (ie. NSAIDs).** In many cases these knock-on effects are harmful rather than helpful and are responsible for many of the negative side effects of the drugs.

In contrast, \( \text{H}_2\text{S} \) as an important player in life’s activities since life’s origins acts holistically. It is a natural, endogenous compound that orchestrates biological events in a coherent manner. **In this way, \( \text{H}_2\text{S} \), when paired with reductionist drugs such as NSAIDs, can act to restore balance and mitigate the harmful aspects.**

**The Many Side Effects of NSAIDs**

NSAIDs are the most widely used drugs in the world. The fact that we use them so often and heavily will come into stark contrast to these drugs inherit drawbacks that we are going to detail. By the time we’re done, you may even question why you take these drugs at all.

The body’s lipid based inflammatory pathway has two branches, COX (cyclooxygenase) and LOX (lipoxygenase). Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) block COX in both its
forms, COX-1 and COX-2, to varying degrees. The difference between different NSAIDs lies largely in the strength with which they block either one or the other and the ratio by which they inhibit COX-1 to COX-2.

COX enzymes metabolize arachidonic acid, a polyunsaturated fatty acid, into various signaling molecules known as prostaglandins. Each form of COX catalyzes arachidonic acid to form its own prostaglandins. COX-1 is constitutive (its concentration in the body remains stable) and creates prostaglandins used for basic housekeeping throughout the body. COX-2, on the other hand, is inducible (normally not present or active in cells but can become so upon stimulation) and produces prostaglandins for the inflammatory response.

Both sets of prostaglandins are important and, while they perform different functions in different tissues - sometimes with opposing effects, both sets are essential to maintain homeostasis. The two sets of prostaglandins need to be in balance or else harmful effects can be effected. For example, in the gastrointestinal tract, COX-1 mediated production of prostaglandins PGE2 & PGI2 plays an important role in regulating the production of bicarbonate and mucus, as well as regulating normal blood flow. COX-1 maintains the normal lining of the stomach and intestines, protecting the stomach from the digestive juices.
In addition, COX-1 signaling is important in maintaining homeostasis of the gut microbiome. Thus, NSAID inhibition of COX-1 can lead to GI side effects such as ulcers and bleeding as well as dysbiosis of the microbiome. For this reason, newer COX-2 inhibitors, which block COX-2 with little effect on COX-1, were developed and have since rocketed in popularity.

However, even selective COX-2 inhibition has its own issues. Specifically, selective COX-2 inhibition causes cardiovascular issues. This is, at least in part, because COX-1 and COX-2 play opposite roles in maintaining vascular homeostasis. Selective COX-2 inhibitors preferentially suppress the vasodilator and platelet inhibitory prostaglandins without blocking the vasoconstrictive and platelet-activating prostaglandins – the overall result being pro-thrombotic. This alteration of hemostasis is at the heart of the toxic side effects of selective COX-2 inhibition seen in drugs like Vioxx and Celebrex.

Furthermore, NSAIDs directly induce the generation of ROS from mitochondria and can thereby directly cause oxidative stress and all the accompanying issues that go along with it (shown below).
Similar harmful side effects are seen in the kidneys as in the cardiovascular system. COX-2 inhibitors reduce renal plasma flow caused by a decrease in prostaglandins, which regulate vasodilation at the glomerular level. NSAIDs disrupt the compensatory vasodilation response of renal prostaglandins to vasoconstrictor hormones released by the body.

Furthermore, the products of COX enzymes not only influence and balance each other, but also influence and balance the products of other inflammatory pathways. For example, Inhibition of COX-2 is thought to lead to an imbalance between two key inflammatory mediators, raising levels of thromboxane A2 relative to prostaglandin E2. This in turn increases production of the previously mentioned pro-inflammatory signaling molecules, the cytokines TNF-alpha (tumor necrosis factor alpha) and IL-1b (interleukin-1 beta). In addition, there is evidence that elevated thromboxane A2 raises levels of an important inflammatory mediator in the LOX (lipoxygenase) pathway, leukotriene B4.

Thus, COX-2 inhibition may help perpetuate the underlying degenerative process while relieving its superficial symptoms. As the scientists who made this discovery put it:

"the short-term effects of (COX-2 inhibitors) on the pain and swelling of inflammation and arthritis may be achieved at the cost of an increased propensity to long-term tissue damage with which these cytokines have been associated."
Wim B van den Berg, another prominent researcher, writes:

“Tumor necrosis factor (TNF) and interleukin-1 (IL-1) are considered to be master cytokines in chronic, destructive arthritis.”

Stimulation of TNF-alpha and IL-1 beta is not the only problem associated with COX-2 inhibitors. The body has two inflammatory pathways, both branching from the inflammatory precursor arachidonic acid. Blocking one pathway while leaving the other wide open is as unbalanced as it is incomplete.

Research has shown that non-selective COX inhibitors create a persistent “rebound effect” on pro-inflammatory signaling. Even two weeks after discontinuation of daily aspirin or ibuprofen, cytokine-stimulated production of TNF-alpha and IL-1 beta was increased from 270% to 538%.

As well, selective COX-2 inhibitors, while producing fewer GI related side effects than COX-1 inhibitors, are not without their gastrointestinal side effects themselves. Whereas it was once thought that COX-2 expression is little to none in the GI tract of humans, this has since been overturned by more recent evidence showing that COX-2 is induced in the GI tract upon proper stimulus.

Figure 19: Source

While COX enzymes are often seen as only inflammatory this is not the case. They play important roles not just in starting inflammatory signaling but also in ending it. This has found to be the case for COX-2 in the GI tract. COX-2 in the GI tract has important anti-inflammatory properties that are vital for the resolution of inflammation and for the recovery and regeneration from injury. Inhibition of COX-2 impairs this anti-inflammatory and regenerative property and thereby can be harmful to the GI-tract.
Thus, GI toxicity is reduced by selective inhibition of COX-2 over COX-1 or pan COX inhibition but not abolished.

It’s important to note that the GI toxicity seen in COX-1 and COX-2 inhibitors extends beyond their impact on the COX enzymes. Even in the absence of COX inhibition NSAIDs can have harmful effects on the GI tract. This COX independent GI toxicity has been found to be due to a mix of interactions. Namely, NSAIDs have been found to interact with phospholipids and uncouple mitochondrial oxidative phosphorylation which initiates biochemical changes that impair function of the gastrointestinal barrier. Furthermore, considerable evidence indicates that interactions among bile, intestinal microbes, and the enterohepatic circulation of NSAIDs are important contributors to the development of NSAID-induced intestinal damage.

Obviously, all of the above raises serious concerns about the safety and efficacy of NSAIDs. And yet, they still do have value. For example, there is no doubt that they are useful for lowering pain and there is even some evidence for their use in reducing the risk of neurodegenerative disorders such as Alzheimer’s Disease. But what if there was a way to mitigate these many side effects, and perhaps increase the efficacy via synergistic effects with the addition of one simple molecule?

Using H₂S to mitigate the side effects of NSAIDs

While COX inhibitors can be thought of as blunt instruments, H₂S on the other hand is more like a conductor who acts to coherently orchestrate biological activities in a holistic manner. Through this yin and yang approach, H₂S can help maintain and restore homeostasis when the system is perturbed by COX inhibitors. And has been shown in Antibe’s earlier studies, H₂S can even incorporate its own benefits to the mix making the resulting combination of NSAID and H₂S more potent than NSAIDs alone, even at a greatly reduced dose.

Whereas COX inhibitors cause a decrease in blood flow as well as bicarbonate and mucus secretion, H₂S acts counter to these actions restoring blood flow and bicarbonate and mucus secretion. H₂S has also been shown to counter act the COX-2 inhibitors promotion of leukocyte adhesion:

“Synthesis of H₂S increases markedly after mucosal injury, and inhibition of H₂S in such circumstances leads to delayed healing and exacerbated inflammation. The beneficial effects of H₂S may be attributable to its ability to elevate mucosal blood flow, prevent leukocyte endothelial adhesion, reduce oxidative stress, and stimulate angiogenesis”

NSAIDs toxic side effects on the GI are not limited to the gut, and unfortunately extend down into the small intestine.

“Nonsteroidal anti-inflammatory drugs (NSAIDs) produce effects during their initial exposure to the small intestine, and when secreted back into the proximal small intestine, along with bile, following their absorption in the distal intestine, and glucuronidation in the liver.”
Once again, the addition of H$_2$S has been shown to alleviate this problem. As seen in ATB-346’s ability to suppress inflammation twice as long at 1/6$^{th}$ the dose, it’s clear that H$_2$S alters the metabolic profile of naproxen. But the benefits of this altered metabolic profile extends beyond the efficacy of ATB-346. Here again we see the addition of H$_2$S, changes naproxen for the better. Specifically, ATB-346 is metabolized in such a way that significantly less naproxen makes its way into the bile, which further reduces the GI related toxicity issues.
Whereas all NSAIDS have the propensity to cause dysbiosis of the gut microbiome, H$_2$S acts to restore a healthy microbial population. In fact, many disorders of the gut such as Crohn’s disease, ulcerative colitis, and inflammatory bowel diseases in general may in fact be adaptive responses of the body due to a disruption of sulfur homeostasis,

“When the “ordinary routes” of sulfur transport and metabolism are not working correctly, the body must find other ways to accomplish the task efficiently. Hence, there appears to be a variety of “back-up mechanisms” to do this which involve modulating the gut bacteria toward a more “dysbiotic” and pro-inflammatory state.”

In these inflammatory bowel conditions the human cells of the gut and the microbial population switch to H$_2$S production in order to provide another energy source to the cells of the gastrointestinal tract and to supply sulfate to the rest of the body. Thus, supplying exogenous H$_2$S could be a means to alleviate these conditions and help to restore stability at the microbiome-mucosa interface,

“As well as reducing GI inflammation and injury and promoting repair, exogenous and endogenous H$_2$S can positively affect many aspects of bacterial-epithelial interactions. There is evidence suggesting potential for the use of H$_2$S donors to favorably modulate the intestinal microbiota. Promotion of biofilm formation and integrity by H$_2$S donors is an important aspect, particularly in the context of improved treatments for disorders such as ulcerative colitis and Crohn’s disease.”

As we have shown and suggested many times over H$_2$S’s effects extend far beyond the GI tract. As such it could help to manage the cardiovascular and renal side effects of COX inhibitors just as it does the GI side effects.

Figure 22: Source - Evolution of Hydrogen Sulfide Therapeutics to Treat Cardiovascular Disease

Whereas, NSAIDs promote the production of ROS from mitochondria H$_2$S promotes mitochondrial health. H$_2$S, depending on the context and concentration, either acts as a as a bioenergetic ‘fuel’ in mammalian mitochondria or as an inhibitor of mitochondrial respiratory activity. In either case, H$_2$S is
acting in a protective manner in an attempt to restore homeostasis, which we have gone to great lengths to show is disturbed with the use of NSAIDs. H₂S further acts in this homeostatic restorative manner by augmenting antioxidant defenses and decreasing mitochondrial heteroplasmy.

Conclusion

H₂S makes a great bed partner for NSAIDs. Not only does H₂S counteract the majority of the toxic side effects associated with NSAIDs, it also brings additional benefits to the body as well. In tandem, these compounds can work synergistically to improve safety and increase the half-life of a single dose, all without sacrificing efficacy. Any one of these improvements on its own would be enough for a breakthrough, but the fact that Antibe with ATB-346 as well as its entire platform can do all of them is nothing short of unprecedented. Furthermore, the mechanism of action of ATB-346, it’s likely that larger and longer term studies will further separate Antibe’s platform from the pack of NSAIDs.

With a market cap of ~$100mm USD, it’s clear that Antibe is underpriced. For now, this company remains under the radar as research into H₂S and its synergistic effects with NSAIDs is still in the early stages. It will take more trials to convince both investors and large pharmaceutical companies that ATB-346 and the company’s platform is as good as we have argued.

Fortunately, we won’t have to wait too long. Antibe is currently running a phase 2b efficacy trial for ATB-346 in patients with Osteoarthritis which is set to read out in early Q2 2020. The company is clearly confident in the potency as the dosages used in the phase 2 trial are as low as 150mg QD. Positive results from this trial have the potential to show to the market and the world that ATB-346 is more effective at reducing pain and inflammation than existing NSAIDs while being orders of magnitude safer.

The last company to come even remotely close to such a feat was NicOx, who paired Nitric Oxide with naproxen to form Naproxcinod. In the end, naproxcinod was not shown to be statistically safer for GI tract. And while naproxcinod did lower BP slightly more than naproxen, it still required the same twice a day dosing for the same level of pain and inflammation reduction. None of these issues stopped Scientific American from naming Naproxcinod as one of the 10 Promising Treatments for World’s Biggest Health Threats in 2006:

“Potential replacement for Vioxx combines the powers of nitroglycerin with those of nonsteroidal anti-inflammatory drugs”

We can only imagine what people will say about ATB-346 and the rest of Antibe’s groundbreaking platform after the company’s phase 2B efficacy results show that the company has found a way to not only make NSAIDs safer but more effective. The market opportunity here is absolutely massive. When Vioxx was discovered to be unsafe, Merck’s market cap fell by $26.8B. In the end, we expect ATB-346 to be much better than Vioxx was ever believed to be.

Disclaimer: This report is intended for informational and educational purposes only. Recipients should consult their own financial and tax advisors before making any investment decisions. This report is not an offer to sell or a solicitation to buy any investment security. The authors may or may not have a position in any security mentioned in this report. The authors are not required to update this report as additional information comes to light.