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The Dichotomy Between Understanding and Treating Emphysema

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1. Introduction

The long history of investigations into the causes and potential treatments of emphysema encompasses a vast array of chemical and biological research disciplines. A key finding that played a major role in initiating these inquiries occurred in 1963 when Laurell and Eriksson[1] found that individuals with a genetic deficiency in serum alpha-1-antitrypsin (AAT) were prone to develop pulmonary emphysema[2]. This genetic linkage was given a mechanistic basis when Turino and colleagues in 1969 discovered that patients with reduced inhibition of pancreatic elastase also lacked serum AAT and were prone to develop severe pulmonary emphysema[3]. Subsequent studies in the early 1970s confirmed that excessive elastase activity due to lack of AAT was in fact the genetic mechanism responsible for the onset of emphysema [4-7]. A key environmental connection was made with the discovery that cigarette smoke increased macrophage secretion of elastase[8] in the lungs, oxidized AAT[9], and that the chemical irritants in smoke recruited neutrophils to the lungs via chemotaxis[10-12]. This integrated genetic-environmental understanding firmly established elastase inhibition as a mechanistic target for preventing the alveolar destruction characteristic of emphysema.

The validation of elastase[13, 14] as a protein target for treating emphysema, motivated three different therapeutic approaches, 1) infusing patients with AAT purified from serum[15], 2) development of small molecule inhibitors[13, 16, 17], 3) novel association of small peptides[18] and synthetic inhibitors [19] with albumin microspheres. The first approach is a biological therapeutic, the second approach is a chemical therapeutic, and the third approach is a prescient recognition that *in vivo* efficacy will likely require long lung residence time pharmacodynamics. The Pharmaceutical industry launched several major multi-decade programs to develop orally available small molecule inhibitors, while apparently completely ignoring the concurrent academic medical research beginning to unravel the complex biology of emphysema and its indication that oral delivery of small molecules was unlikely to have any therapeutic benefit. Interestingly, a completely different basic research discipline, X-ray crystallography, had a seminal impact on the class of molecules from which Zeneca derived their clinical candidate. The first structure[20] was solved In 1976 by Alber, Petsko, and Tsernoglou, which showed atomic resolution details of

elastase digesting a substrate. Sawyer and colleagues deposited the first high resolution crystal structure of porcine pancreatic elastase[21] into the protein data bank, and in 1982 Hughes and colleagues[22] solved a structure of the enzyme bound to a trifluoroacetyl dipeptide inhibitor (deposited in the PDB in 1986), thus making high resolution structures with and without bound ligand available to the research community. The trifluoroacetyl motif (shown in Figure 1) became a cornerstone of Zeneca's small molecule research program[23-32], which resulted in the clinical candidate ICI 200,880[33]that was halted due to lack of efficacy in Phase II clinical trials.

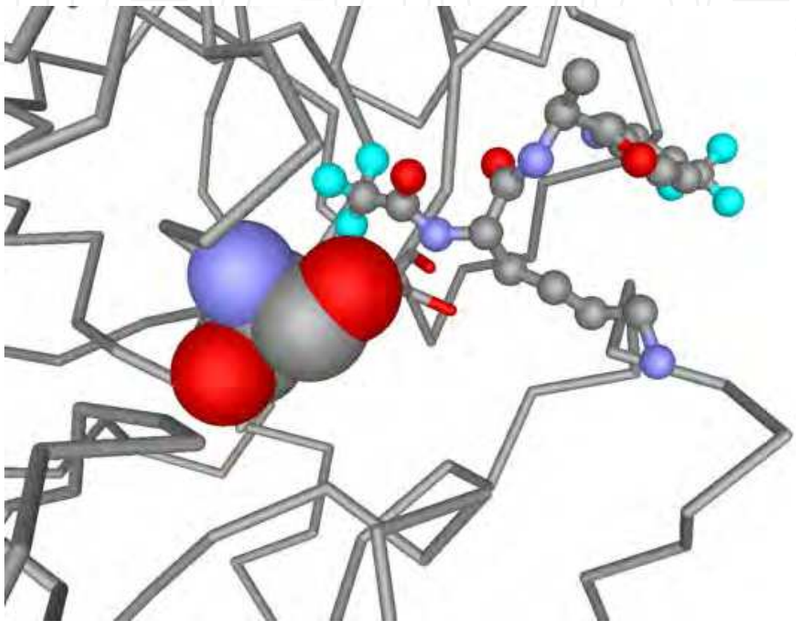

Fig. 1. Co-crystal structure taken from the protein data bank file 2EST. This structure shows the catalytic serine (shown in space fill) performing a nucleophilic attack on the carbon of the ketone attached to a trifluoromethyl group – the fluorines are shown in light blue. The highly electronegative fluorine atoms significantly enhance the electropositive nature of this carbon and hence trifluoromethyl-ketone molecules have a high affinity for elastase.

Even as the first therapeutics were being developed, a report on neutrophil lung recruitment via elastin peptide chemotaxis [34] gave the first indications of the complexity and immunological involvement [35] in the development of pulmonary diseases. Elastase digests elastin resulting in peptide fragments that elicit circulating neutrophils to enter the lungs. These neutrophils secrete fresh elastase causing new lung damage, new elastin peptide fragments and recruitment of new neutrophils again secreting fresh elastase into the lungs in a destructive feedback loop. These studies already presented evidence that inhibiting elastase in the short term would be insufficient to treat emphysema. Compounding the complexity, early elastase inhibitors administered intraperitoneally that showed promise in stemming emphysema, cleared rapidly [36] *in vivo* with concomitant renal nephropathy [17]. The complex interplay between lung injury and immune response that begins with a single intratrachael instillation of elastase motivated many detailed studies aimed at elucidating the basic biology of emphysema progression. Early key findings on the long term effects on lung tissue of only one exposure to elastase includes, 1) ultrastructural changes occurring 16

days later [37], 2) dose related changes in pulmonary function after 4 weeks [38], 3) 14 day lung residence time of the enzyme complexed with alpha-macroglobulin [39], 4) resistance to AAT inactivation in the presence of activated neutrophils [40], 5) uptake by alveolar macrophages with subsequent re-release of elastase [41]. Additionally, activated neutrophils can secrete elastase for over 12 days [42].

2. Lessons from the Stone lab

While the complex biology of emphysema most likely precludes treatment using a simple small molecule elastase inhibitor strategy, important physiological parameters essential for developing an effective therapeutic modality were reported by Stone and Lucey between 1988 and 1991. These investigators showed that, 1) one intratracheal dose of elastase causes maximum damage after 4 weeks [43], 2) a potent elastase inhibitor given intratracheally in 170-fold molar excess has a lung half-life of 4 minutes (Figure 2) and actually results in worse emphysema relative to animals given saline with no elastase [44], 3) covalently linking an active small molecule to a polymer of hydroxyethyl-aspartamide (stationary phase for hydrophilic column chromatography) results in a lung half-life of 441 minutes and amelioration of elastase induced emphysema [45]. This collection of results indicates that long lung residence time is an essential component of any meaningful emphysema treatment and that elastase must be down-regulated continuously for at least 4 weeks.

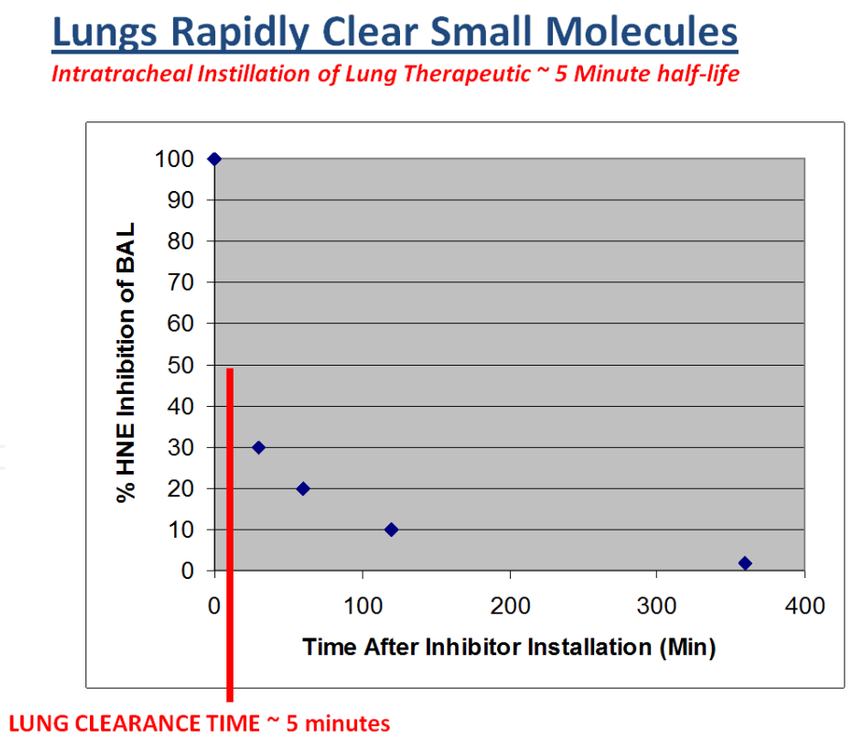

Fig. 2. This is a recreation of the data from Phil Stone's lab showing that small molecule elastase inhibitors have a lung half-life of 4-5 minutes. It is important to understand that these experiments were conducted by intratracheally instilling the small molecule elastase inhibitor and thus 100% of the dose was initially deposited into the lungs. Small molecules administered orally will result in only a tiny fraction of the dose ever actually entering the lungs.

3. Combining inhibitors with surfactant replacement therapy

Even though Zeneca's clinical candidate ICI 200,880 was halted in Phase II clinical trials for lack of human efficacy, the molecule possessed two essential features of a drug, 1) high affinity anti-elastase activity, and 2) it was deemed safe to give to humans as evidenced by passing Phase I clinical trials. When the small molecule chemistry work of Zeneca is combined with the *in vivo* biology work of Phil Stone, the logical conclusion is that an efficacious *in vivo* emphysema treatment requires that ICI 200,880 somehow be recast so that it spreads across the vast surface area of the lungs and resists being expelled into systemic circulation. If such a recasting could be achieved, the long lung residence time could result in an immune response, thus ultimately negating the treatment. So the next logical step places the strong constraint that any adjuvant molecule used to do the recasting must naturally reside in the lungs. A natural lung molecule that has the intrinsic properties of spreading across the vast surface area of the lungs is a defining property of the lung surfactants.

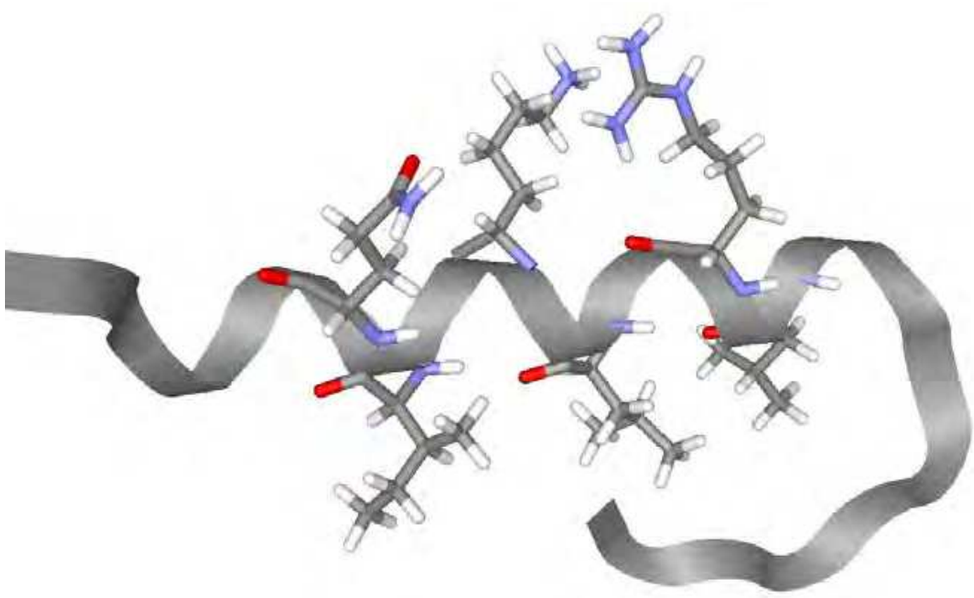

Fig. 3. NMR structure of residues 1-25 from the N-terminal of surfactant peptide B taken from the protein data bank file 1DFW. An important feature of this peptide is its amphiphilic structure as illustrated by having one face composed of hydrophobic residues and the opposite face composed of charged and hydrophilic amino acids.

Human lung surfactant is a complex mixture of lipids and peptides that was extensively studied in the 1980s when it was realized that delivering surfactant harvested from animals to the lungs of severely pre-term infants is a life-saving [46-52] procedure. Early biophysical studies of lung surfactant indicated that it was ~90% lipids and ~10% protein by weight [53]. Detailed analysis showed that the protein component was actually made up of 4 different molecules, 2 larger hydrophilic proteins and 2 smaller hydrophobic proteins [54, 55]. Remarkably, when 1% or 0.1% by weight of the smallest of these proteins isolated from lavage fluid was added to synthetic phospholipids, both mixtures essentially eliminated dynamic surface tension in biophysical experiments [56, 57], a result that the investigators admitted was truly startling. The protein with such astounding surface active properties is a 79 residue

peptide now called surfactant protein B. What is even more amazing is that subsequent biophysical studies demonstrated that the first 25 amino acids possesses essentially identical surface active properties[58, 59] to the whole protein (Figure 3). Further confirmation of the importance of the first domain of surfactant protein B comes from Discovery Labs with their Phase III clinical studies that one dose of $(Lys\text{-}Leu\text{-}Leu\text{-}Leu)_4$ [60] a mimetic of SP-B 1-25 added to cow lavage dramatically reduces mortality in severely preterm infants [61].

4. Conclusion

The long, involved, complicated history of emphysema integrates genetics, protein and small molecule therapies, medicinal chemistry, crystallography, biophysics, and several other research disciplines. Interestingly, all of this complexity can lead to a rather simple conclusion - that covalently linking Zeneca's clinical candidate to the first 25 residues of surfactant peptide B (Figure 4) would be an effective long acting anti-emphysema treatment if delivered intratracheally. When these studies were carried out[62], one dose of the SP-B (1-25)-Zeneca peptide-small molecule construct completely protected rodents exposed to near lethal doses of the human neutrophil elastase for 4 weeks (Figures 5&6). Of course it remains to be seen whether or not this simple idea will prove to be efficacious in humans, because recent studies have demonstrated that AAT plays a complex multifactorial role in the recruitment of neutrophils into the lungs. For example, Li[63] and colleagues have demonstrated that oxidized AAT induces lung epithelial cells to release IL-8, resulting in CXCR1 mediated neutrophil chemotaxis into the lungs, while Bergin[64] and coworkers have shown that glycosylated AAT sequesters IL-8 disrupting activation of CXCR1 and neutrophil mobilization. To further complicate matters, calpain[65] induces TNF-alpha mediated neutrophil chemotaxis and AAT binds to and inhibits calpain[66] thus preventing lung neutrophil infiltration by yet another mechanism. Even with all of this complexity and its implications that antioxidant therapy may be beneficial, the long established destructive role of unchecked elastase activity makes this enzyme a central target for inhibiting the progression of the alveolar wall destruction characteristic of emphysema as evidenced by the extensive pharmaceutical development that has gone into this endeavor, which includes small molecules from ONO[67], Merck[68], Zeneca[24], and Glaxo[69] (Figure 7).

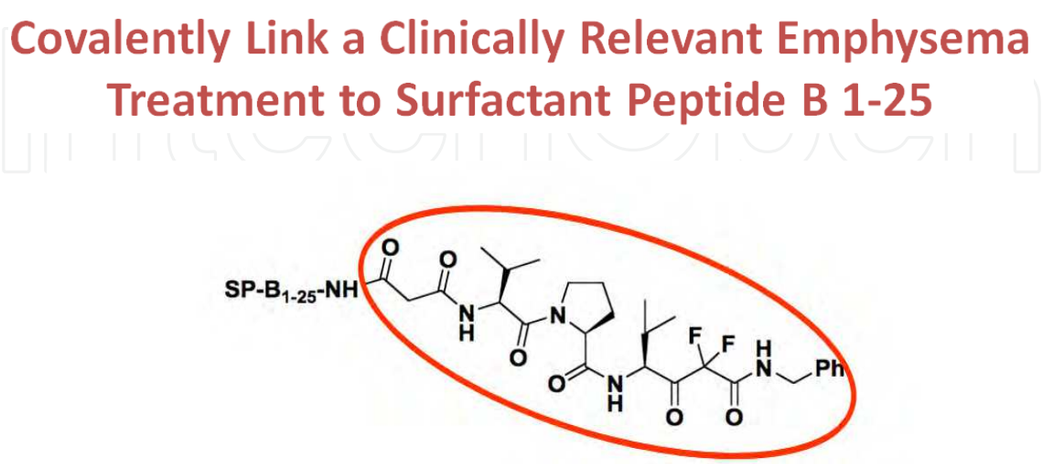

Fig. 4. A small molecule from the Zeneca family of fluoro-peptidomimetics covalently linked to the N-terminal of the first 25 residues of surfactant peptide B.

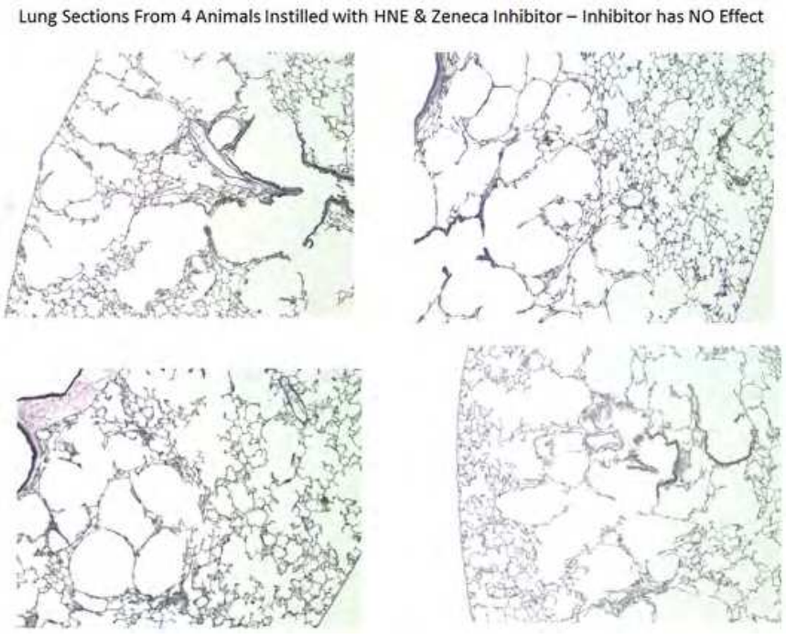

Fig. 5. Emphysema is induced in rodents by intratracheally instilling human neutrophil elastase. When elastase is administered with a potent Zeneca small molecule inhibitor, the rodents develop emphysema after 4 weeks to the same degree as rodents given no inhibitor. The small molecule was in 70-fold molar excess concentration relative to elastase.

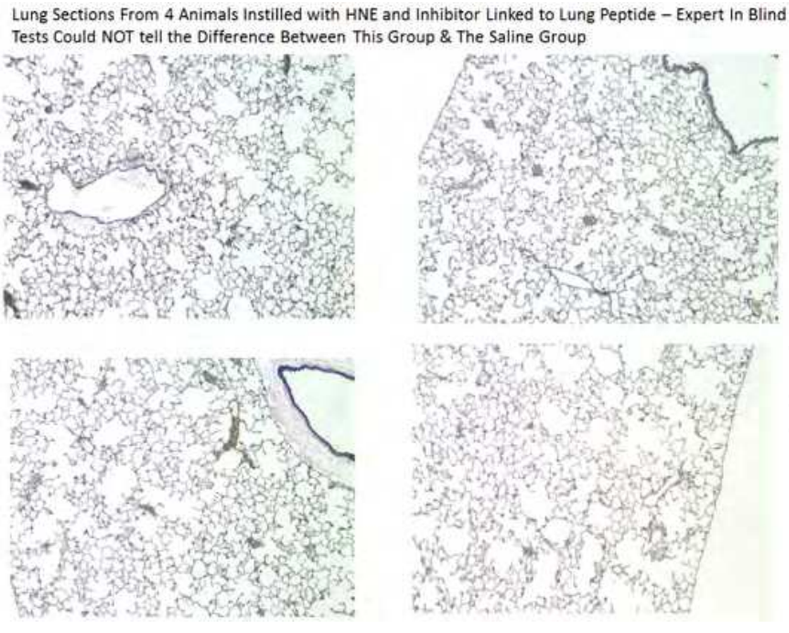

Fig. 6. When this exact same small molecule was covalently linked to the fragment of surfactant peptide B as shown in Figure 4, one dose given in 30 fold molar excess completely protected the animal for 4 weeks. All animals were dosed with a mixture of HNE and either the Zeneca small molecule or the Zeneca small molecule covalently attached to the surfactant peptide and sacrificed after 4 weeks.

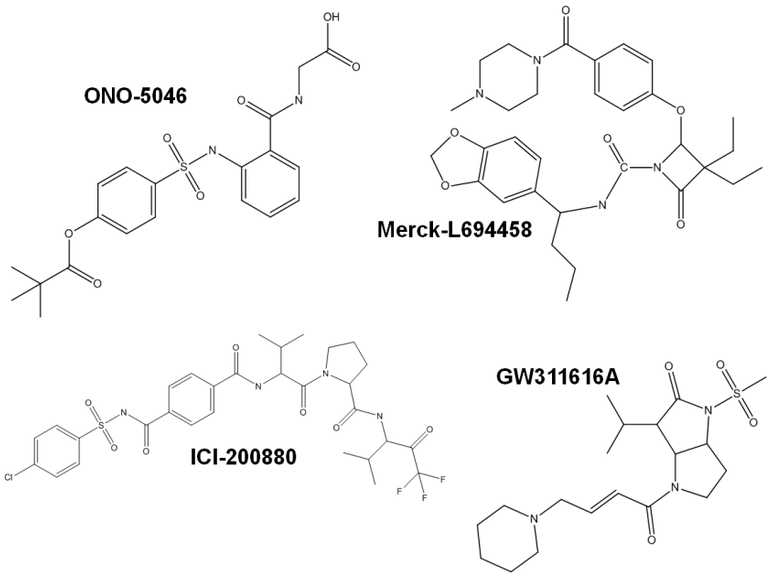

Fig. 7. Small molecule elastase inhibitors from ONO, Merck, Zeneca, and Glaxo.

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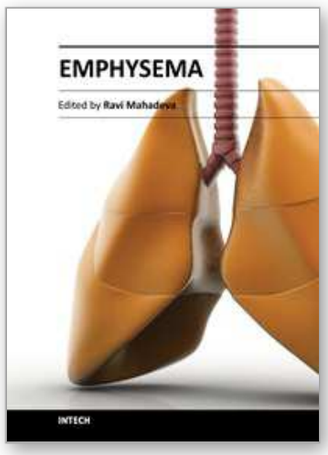

Emphysema

Edited by Dr. Ravi Mahadeva

ISBN 978-953-51-0433-9
Hard cover, 134 pages
Publisher InTech
Published online 30, March, 2012
Published in print edition March, 2012

Chronic Obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality world-wide. The most common cause is chronic cigarette smoke inhalation which results in a chronic progressive debilitating lung disease with systemic involvement. COPD poses considerable challenges to health care resources, both in the chronic phase and as a result of acute exacerbations which can often require hospital admission. At the current time it is vital that scientific resources are channeled towards understanding the pathogenesis and natural history of the disease, to direct new treatment strategies for rigorous evaluation. This book encompasses some emerging concepts and new treatment modalities which hopefully will lead to better outcomes for this devastating disease.

How to reference

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Frank Guarnieri (2012). The Dichotomy Between Understanding and Treating Emphysema, Emphysema, Dr. Ravi Mahadeva (Ed.), ISBN: 978-953-51-0433-9, InTech, Available from: http://www.intechopen.com/books/emphysema/the-dichotomy-between-understanding-and-treating-emphysema

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