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MEETING REPORT

Highlights of the Society for Medicines Research symposium held on September 11, 2007, at the Wellcome Trust Conference Centre, Hinxton, Cambridge, U.K.

Emerging Therapies for Respiratory Diseases

by Ruth Lock, Steve Collingwood and Andrew Ratcliffe

Summary

This Society for Medicines Research symposium, sponsored by UCB, was held on September 11, 2007, at the Wellcome Trust Conference Centre, Hinxton, Cambridge, United Kingdom. The meeting, organized by Ruth Lock, Steve Collingwood and Andrew Ratcliffe, reviewed current thinking in the area of airway drug delivery and the challenges and progress made in the discovery and development of novel medicines to treat respiratory diseases, such as chronic obstructive pulmonary disease, asthma, allergic rhinitis and cystic fibrosis.

The classes of drugs licensed to treat respiratory diseases has not dramatically changed over the last 25 years. Nevertheless, as unmet medical need is still high, this disease area is still the subject of intense research efforts by the pharmaceutical industry and academia. Inhalation as a delivery route offers unique advantages, with more recent advances including the potential for once daily dosing.

Professor Clive Page (Sackler Institute of Pulmonary Pharmacology, Kings College, London, U.K.) delivered the opening lecture in which he discussed challenges facing the development of new drugs for the treatment of airway diseases. Respiratory diseases still remain a considerable burden to society, with asthma, chronic obstructive pulmonary disease (COPD) and cough remaining diseases with unmet medical needs. Around 150 million people worldwide suffer from asthma, and both the incidence and the mortality rate of the disease continues to rise. Short-acting β_2-adrenergic agonists, such as **salbutamol**, were introduced in the 1960s and act as symptom controllers of the disease. The glucocorticosteroids were introduced in the 1970s and remain the mainstay of asthma treatment, controlling the underlying inflammation. β_2 agonists cannot be used as a monotherapy since they do not possess clinically important antiinflammatory activity, and so fail to control the underlying disease process. Combinations of inhaled corticosteroids and long-acting β_2 agonists are becoming more widespread for patients with moderate to severe persistent asthma: the most common combination currently in use is **fluticasone propionate/salmeterol** (*Advair*® in the United States, and *Seretide*® in the United Kingdom). Another combination is **budesonide/formoterol** which is commercially known as *Symbicort*®. However, significant concerns remain over the use of inhaled glucocorticosteroids to treat a disease often starting in children under 5 years old, and recently "Black Box" warnings have been added to the labels of all medicines containing long-acting β_2 agonists (LABAs). Concern was expressed over the new ultra LABAs that are being developed by many of the leaders within the industry. Despite the availability of improved steroids, corticophobia has led to the success of Merck & Co.'s orally active leukotriene receptor

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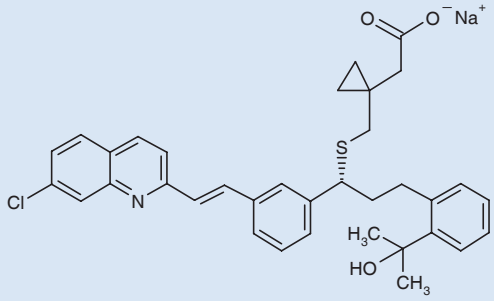


Montelukast

antagonist **montelukast** (*Singulair*®), particularly in the United States. An interesting question centered on whether oral therapy (not yet safely developed) would be preferred over inhaled counterparts.

Over the past 25 years, various theories of the cause of asthma, including the critical role of the eosinophil, have been disproved by the failure of new therapies (for example, anti-interleukin [IL]-5 and IL-12 agents) in the clinic. The role of sensory nerves in allergic rhinitis has been established, with the suggestion that they could also contribute to the irritability of the respiratory tract observed in asthmatics. Treatments targeting the potential neuronal aspects of asthma might prove fruitful, possibly by exploitation of targets such as TRPV1, 5-HT_3 or P2X gated ion channels. RSD-931 (**carcainium chloride**), which acts on delta fibers and was previously under investigation by Cardiome as a potential treatment for chronic pain, shows some promise in some animal models.

COPD is a group of diseases characterized by the pathological limitation of airflow in the airway that is not fully reversible. Whilst the disease is very different to asthma the treatments that are available are similar. For treatment of the symptoms of COPD both short- and long-acting β_2 agonists, along with M_3 muscarinic antagonists (anticholinergics), are widely used. Controversy still remains regarding the precise role of the glucocorticosteroids in COPD. Professor Page explained that there is growing recognition that COPD has a major systemic component which could provide future opportunities for new approaches of treatment. Such new therapies could include orally acting antiinflammatories, therapies inhibiting emphysema and therapies influencing mucous plugging.

Drug delivery to the lungs: problems and opportunities

Professor Chris O'Callaghan (Institute of Lung Health, University of Leicester) delivered the second lecture, which from a clinician's perspective focused on the problems and opportunities of drug delivery to the lungs. The most common use of aerosolized drugs is in the treatment of asthma. The drug treatment regimen for the majority of patients is uncomplicated, but clinicians are frequently confused by the ever increasing choice of drug delivery devices, and quite often there is insufficient published information for such devices. In addition, drug delivery devices are not strictly regulated by governmental bodies and many, such as nebulizers and spacers, can be bought over the counter. Depending on the choice of device the amount a patient may inhale can vary by four- or five-fold.[1,2] For drugs that have a narrow therapeutic index this is a significant problem, especially since many devices are used inappropriately by the patient. Drug delivery to children is further complicated, where a combination of spacer and facemask, spacer alone, dry powder inhaler or nebulizer can be selected depending on their age.

Estimation of drug delivery to young children is also difficult. Ethically it is difficult to collect fluids from children in order to understand the pharmacokinetics following inhalation. Also, whilst scintigraphy of the lungs following administration of radiolabel is commonly used in adults to follow pulmonary distribution, again, ethically, administration of radiolabel to children is problematic since drug deposits in hotspots in the lung, and this would need to be quantified and the associated risk explained to parents. For an inhaled gene therapy this may be acceptable, but not for a treatment such as an inhaled β_2 agonist.

Control of the upper airway is key to effective drug delivery to the lung. The efficiency of the device plays a role, as does the technique of delivery by the patient. A series of short videos highlighted the issues of dry powder inhaler administration by patients, and how the interaction between the patient and device is essential for good drug deposition and reproducibility. Unlike adults, children will inhale through the nose and mouth. Treatment failures can be problematic in children. For example, during emergency administration via a facemask, holding the facemask just 2 cm from the child's face during the nebulization period can reduce delivery to the lung by around 80%.

Although drug delivery to the lung can be problematic, the large surface area of the central airways, combined with good epithelial permeability, provide the opportunity for the lungs to act as a portal for systemic delivery. A number of therapies are currently under development aiming to take advantage of the high bioavailabilities and rapid onset of action potentially provided by pulmonary delivery. Examples include the delivery of macromolecules (peptides and proteins) such as insulin, and the delivery of an inhaled vaccination for measles. An inhaled form of the measles vaccine for mass inoculation programs in developing countries would reduce

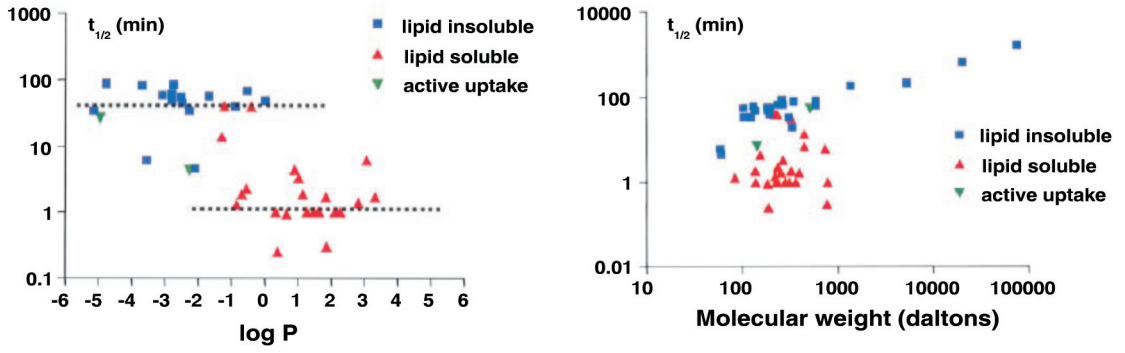


Fig 1. Pulmonary absorption data from Schanker and colleagues.[3,4](Graphs reproduced with permission from Patton, J., Fishburn, C. and Weers, J. *The lungs as a portal of entry for systemic drug delivery.* Proc Am Thorac Soc 2004, 1(4): 338-44. (c) American Thoracic Society.)

the risk of HIV (through needle exchange). Currently, the vaccine needs to be stabilized against heat to protect against degradation. Understanding the amount delivered to the patient of such therapies is essential, particularly for those medications that have a narrow therapeutic index.

Mechanisms of drug retention in the lung

The challenge of targeting lung retention with small molecules was discussed by Dr. Douglas Ferguson (AstraZeneca, Charnwood). In recent years there has been a resurgence within the industry in inhaled drug delivery both for topical treatment of lung disease and for systemic delivery of macromolecules (and other systemically acting drugs with low oral bioavailability). The lung has several key properties which make it an attractive option for rapid systemic delivery with high bioavailability—large surface area, high epithelial permeability, low volume of epithelial lining fluid, thin alveolar/capillary membrane, low metabolic activity and high perfusion rate.

These same properties make it very difficult for the preclinical scientist to try to design small-molecule drugs that will be retained by the lung at their site of action. If the goal is to overcome low oral bioavailability or achieve rapid onset, then duration ($t_{1/2}$) may be optimized by normal systemic pharmacokinetic approaches: an appropriate combination of clearance and volume of distribution. Where inhalation is being considered as a route to try to minimize unwanted systemic side effects, then a different strategy is required.

Ideally, topical delivery would result in free concentrations at the effect site in the lung that are higher than the corresponding concentrations in the rest of the body, with the separation in free concentration being maintained throughout the dosing interval. High systemic clearance can be used to minimize systemic exposure, but this can also drive removal of free drug from the lung. So how do we retain drug in the lung tissue? Reviewing the available literature on pulmonary absorption rates in preclinical species reinforced the challenge of targeting lung retention. Decreasing lipid solubility and increasing molecular weight can lead to a longer pulmonary absorption $t_{1/2}$, but on average absorption was still rapid with $t_{1/2abs}$ approximating 60 minutes (Fig. 1). Very high molecular weight (>10,000 daltons) was required to slow absorption considerably.[3,4]

Apparent strategies for retaining drug in the lung are published in the literature. These include lowering permeability[6] (useful for reducing blood C_{max}, but difficult to achieve once-daily doing using this strategy alone), slow dissociation from the target receptor[7,8] (tiotropium bromide vs. ipratropium bromide—challenging preclinically from a pharmacokinetic perspective), slow dissolution rates[9] (fluticasone propionate vs. budesonide, again, important for lowering C_{max} systemically but duration observed clinically for fluticasone propionate related to its higher volume of distribution compared with budesonide and not its slower dissolution[10]), high tissue affinity (basicity and specialized trapping mechanisms such as lysosomal trapping, mitochondrial binding) and fatty acid esterification[11] (budesonide).

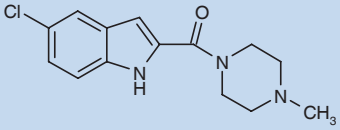
It is clear that inhalation continues to be a developing field in terms of modern drug metabolism and pharmacokinetic (DMPK) approaches/rational drug design (despite is long history). Specialized lung retention mechanisms appear common in marketed inhaled drugs. Often only a fraction of the administered lung dose is actually retained. Several mechanisms retain the drug in the lung within a depot—in which the drug may not be free to interact with the receptor. Such mechanisms can prolong the $t_{1/2}$ in the lung but may only contribute modest improvements in terms of local versus systemic selectivity. Free drug within the lungs will still be subject to rapid absorption and any lung:plasma free concentration gradient will largely be determined by the systemic clearance and permeability.

Histamine H_4 receptor antagonists

Dr. Richard Hale (Cellzome, U.K.) described Cellzome's success at identifying a potent and selective histamine H_4 receptor antagonist for the treatment of allergic rhinitis. Histamine was first isolated chemically by Sir Henry Dale in 1910, and this led to histamine research being at the forefront of drug discovery and rational drug design. The first antihistamine to be used in humans was phenbenzamine in 1942. This was replaced by mepyramine, which is still in clinical use. The antihistamines developed in the 1940s were widely used in the treatment of allergic rhinitis and urticaria. However, they were unable to block all of the actions of histamine, including the stimulation of gastric acid secretion and by 1949 it was concluded that there were two histamine receptors. In 1972, Sir James Black and colleagues at Smith-Kline & French identified the second histamine receptor and its interaction with burimamide. Developments to improve toxicity and oral activity led to identification of cimetidine, to treat acid-related gastrointestinal diseases like peptic ulcers. In 1983, pharmacological techniques were used to identify a further receptor subtype, H_3, in the brain, and this now represents an interesting target for a number of central nervous system (CNS) conditions. In the early 1990s the genes for the histamine H_1 and H_2 receptors were cloned, but it took until 1999 to clone the gene for the histamine H_3 receptor.

The fourth histamine receptor (H_4) was identified in 2000, following the human genome sequence. Around eight different groups published its discovery at about the same time. It is expressed in many cells of the immune system and is coupled to cell migration. Antagonism at the H_4 receptor may be antiinflammatory, giving rise to the third generation class of antihistamines. Much of the pioneering work has been carried out by Johnson & Johnson using their potent and selective antagonist **JNJ-7777120**,[12] and the histamine H_4 receptor has potential as a target in a number of diseases,[13,14] including allergic rhinitis, asthma, atopic dermatitis, colitis and pruritus. However, there are major differences in histamine receptors and biology across animal species. These show themselves as differences in affinity for histamine and other ligands, as well as differences in efficacy and biological outcome. Furthermore, H_4 receptors show a greater difference between species than other histamine receptors. Therefore, selection of appropriate animal models which might predict human pharmacology and dose selection is particularly difficult. Consequently, clinical data will be critical to the understanding of the relevance of the H_4 receptor as a drug target.

Dr. Hale described the development of Cellzome's lead candidate, **CZC-13788**. The research program was originally licensed from Argenta Discovery at the hit phase. Cellzome and Argenta scientists worked together during the early parts of the lead optimization. The objective of the project was to develop a potent and selective histamine H_4 receptor antagonist and develop the molecule into clinical testing. CZC-13788 is a potent and selective small-molecule H_4 receptor inverse agonist which is currently in preclinical development. All current marketed H_1 and H_2 antihistamine drugs are inverse agonists. It is effective in human blood and animal models, and is able to inhibit histamine driven shape changes in human eosinophils. It has a pharmacokinetic profile consistent with once daily oral dosing and a good toxicity profile. CZC-13788 will primarily be evaluated in allergic rhinitis in man (first-in-man mid-2008). This choice of indication has been prompted by the fact that allergic rhinitis represents the most direct route to a clinical assessment of pharmacodynamics, and perhaps efficacy. The target has never been assessed in humans and remains the key uncertainty for the development program. In addition, it is Cellzome's intention to out-license the product, since the company's primary focus is not on developing novel therapeutics.



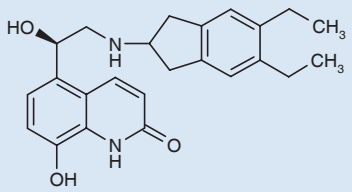
JNJ-7777120

Long-acting β_2-adrenoceptor agonists

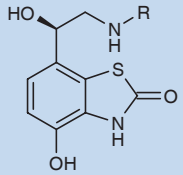
To relieve the compliance of using multiple inhalers several times a day, Dr. Robin Fairhurst (Novartis Institutes for Biological Research, U.K.) described efforts towards the identification of an inhaled once-daily β_2-adrenoceptor agonist for the treatment of asthma and COPD. Central to the underlying strategy was the design of drugs both basic and lipophilic in nature, so as to aid rapid onset of action and retention in the airways, but also subject to high first pass hepatic clearance to limit unwanted systemic effects. **Indacaterol** is the lead candidate from the project, which is currently undergoing phase III clinical studies. In the search of new leads, efforts turned to a series represented by **(1)**, in which the 4-hydroxybenzothiazolone unit served as a catechol mimic to facilitate rapid clearance, and whereby efficient optimization of the basic N-substituent could be undertaken by ring opening of the intermediate chiral epoxide **(2)** with primary amines.[15]

In addition to using amines of the β-phenethyl type, which represent a well-established β_2-adrenoceptor N-substituent, a structurally diverse set of amines from commercial sources and the Novartis archive were also selected in the search of adding further novelty and interesting structure-activity relationships. Amines were sourced based on the highest probability of delivering the desired duration and onset of action in an *in vitro* guinea pig tracheal assay.

In the case of the β-phenethylamine class of 4-hydroxybenzothia-



Indacaterol



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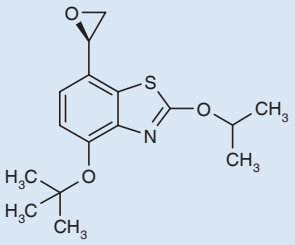


(2)

zolones, a significant proportion of analogues elicited potent β_2 agonist activity, with >50-fold selectivity against the β_1-adrenoceptor at the functional level. Likewise, within the diverse amino substituted class of 4-hydroxybenzothiazolones, a similar high percentage of compounds proved to be highly active agonists. The α-substituted cyclopentylamine moiety provided a versatile opportunity, in the form of multiple stereoisomers, to tune potency, intrinsic efficacy and side effect profile to the level of indacaterol.

Of the 100 most active 4-hydroxybenzothiazolones derivatives, 46 were deemed too potent for ready formulation. To counter this, 5-hydroxybenzothiazolone analogues were devised, which exhibited a 6- to 50-fold potency shift to lower K_i's. However, several of these still delivered β_2 agonists falling within the optimal potency range with acceptable intrinsic efficacy, thereby providing further compounds for profiling.

Cystic fibrosis—potentiators and correctors

Cystic fibrosis is the most common fatal genetic disorder among Caucasians and is characterized by enhanced mucus accumulation in the lung with accompanying microbacteria infections that ultimately leads to mortality. Mutations in the cystic fibrosis transmembrane regulator (CFTR) are responsible for the disease. The most prevalent is deletion of phenylamine at position 508 (ΔF508-CFTR), which interferes with protein folding, trafficking to the apical membrane, membrane stability and channel gating. In addition to ΔF508-CFTR a further mutation of note is G551D, which results in defective gating but with little effect on trafficking.

Dr. Frederick Van Goor (Vertex Pharmaceuticals, San Diego, California, U.S.A.) presented upon Vertex's efforts to pharmacologically rescue core defects in multiple CFTR mutations. Using an optical membrane-potential based high-throughput screening assay, with apical chloride anion secretion from diseased airway epithelia cells as a readout, modulators of ΔF508-CFTR were identified. These could be subclassified into potentiators, small molecules that increased PKA-regulated chloride anion channel gating of CFTR, or correctors, small molecules that rescued the folding and trafficking of ΔF508-CFTR.[16] Of the two classes, a greater hit rate for potentiators was observed.

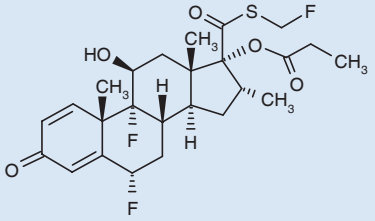
Hit to lead optimization of the potentiator high-throughput screening hit VRT-484 (EC_{50} = 1720 nM) led to single digit nanomolar activity in VRT-159 (EC_{50} = 3 nM). Unfortunately, poor oral DMPK precluded further progression. This was solved in **VX-770** (EC_{50} = 3 nM), which exhibited excellent DMPK properties across species, with the desired selectivity against other ion channels and cAMP signalling. VX-770 restored chloride anion secretion in G551D/ΔF508 human bronchial epithelia to approximately 60% normal. Phase I studies in both healthy and cystic fibrosis patients completed in 3Q 2006, and the drug has been granted orphan and fast track designation. Currently, phase IIa multicenter, randomized, double-blind and placebo-controlled clinical studies are on going. A key question going forward is whether VX-770 will impact established lung disease, and which cystic fibrosis patients will respond.

VRT-325 is representative of a modulator that corrects CFTR processing and trafficking, and increases ΔF508-CFTR stability. The series is currently in the final stages of lead optimization with potent, efficacious and drug-like molecules identified.

Direct readout of ΔF508-CFTR correction in patients, which could represent a clinical biomarker, remains a future challenge, as well as whether a dual potentiator/corrector combination therapy, which appears to work in synergy in increasing chloride anion secretion in ΔF508-CFTR human bronchial epithelia to greater levels than observed in non-CF human bronchial epithelia, will add superior clinical benefit.

Novel glucocorticoids

Glucocorticoids represent one of the mainstays of inhaled and intranasal therapy for a number of airway diseases. After the initial discovery of the antiinflammatory activity of cortisol, key progression phases in glucocorticoid receptor (GR) therapy have centered on optimizing inhaled and intranasal delivery (**beclomethasone dipropionate**), coupled with enhanced systemic inactivation (**fluticasone propionate**). More recent advances have focused on combination therapy

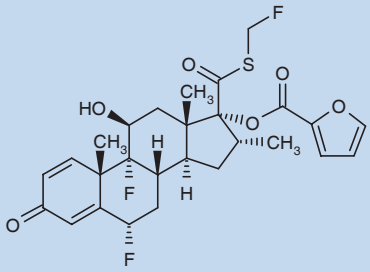


Fluticasone propionate

with β_2-adrenoceptor agonists (fluticasone propionate + salmeterol).

The GR belongs to the nuclear receptor superfamily and has significant homology with other steroid receptors, including mineralocorticoid receptor (MR), progesterone receptor (PR) and androgen receptor (AR). In its apo form it is held in an inactive state within the cytoplasm by chaperone proteins. Ligand binding results in dissociation of the protein complex and translocation of the activated GR to the nucleus, where it can regulate the expression of multiple genes either positively (transactivation, TA) or negatively (transrepression, TR). The desired antiinflammatory activity of glucocorticoids appears to be driven primarily by TR of proinflammatory genes. In contrast, many of the associated side effects appear to emulate from TA processes. Although the GR activity of fluticasone propionate is over a log higher than PR activity, excellent selectivity over MR and AR is attained. However, no selectivity is observed with respect to the TR/TA axis, in line with other currently used glucocorticoids.

Dr. Keith Biggadike (GlaxoSmithKline, Stevenage, U.K.) described efforts to design GR modulators, in particular with improved selectivity against PR, and with a degree of dissociation for the TR pathway over the TA pathway in the hope of imparting a greater therapeutic index. A crystal structure of fluticasone propionate in GR revealed binding of the 17-α propionate in a lipophilic pocket, the latter of which appeared less apparent in PR and MR structures. The volume of the pocket suggested scope for further optimization, and to this end a series of 17-α heteroaryl esters were synthesized that retained high GR potency as full agonists. From this work, **fluticasone furoate** emerged as a superior agent to fluticasone propionate in a number of *in vitro* and *in vivo* GR assays, leading to its development as an intranasal drug recently launched as *Veramyst*™.[17] A crystal structure of fluticasone furoate in GR confirmed



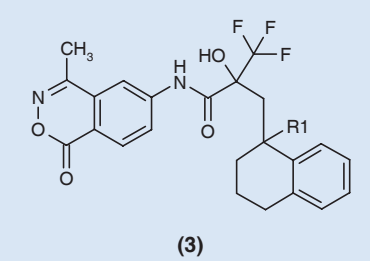
Fluticasone furoate

the furoate ester as more fully occupying the lipophilic 17-α pocket.

Saturation of the 17-α heteroaryl esters, in conjunction with further modifications, led to GR agonists with a similar potency to fluticasone propionate but with greatly enhanced GR/PR selectivity ratios (>1,000-fold). A similar profile resulted with a series of 17-α alkyl carbonates, but with the added milestone of significant TR/TA selectivity.

To date, clinically used glucocorticoids in the airway field have been designed primarily for topical administration. In the search for oral medications focus has shifted to the discovery of nonsteroidal glucocorticoids that display selectivity for TR over TA, and where physical and molecular properties can be better optimized for oral delivery and DMPK. Manual agreement docking of a published series of nonsteroidal ligands into the GR structure revealed a single agreed binding mode that resulted in the design of **(3)** (R1=H), which exhibited potent GR binding but only partial agonism at the submicromolar level.

Further exploration around the tetrahydronaphthalene ring system



(3)

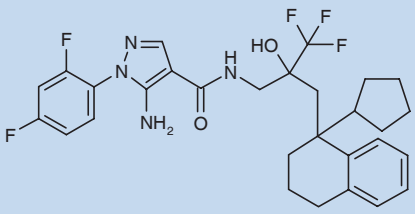
revealed that replacement of R1=H in (3) with alkyl and cycloalkyl groups resulted in an agonism trigger, with compounds exhibiting three orders of magnitude increase in potency and behaving as full agonists. More importantly, further studies demonstrated the desired dissociation profile sought of TR over TA.[18]

Unfortunately, the benzoxazinone ring system, which acts as a steroidal A-ring mimetic, proved chemically intractable and vulnerable to metabolism. Using 3D pharmacophore searching, in conjunction with an array synthesis approach, aryl pyrazoles were discovered as an A-ring mimetic. Although early compounds showed good GR binding they lacked agonism. Following two further iterations, including incorporation of the agonism trigger, analogues such as **(4)** were discovered that elicited potent full GR agonism, with reduced TA efficacy and outstanding selectivity over AR, PR and MR.[19]

Long-acting muscarinic receptor antagonists

COPD patients show symptomatic relief when treated with peripherally acting muscarinic antagonists. Short–(**ipratropium bromide**) and long-acting (**tiotropium bromide**) inhaled agents are currently in clinical use. Although the muscarinic family comprises five receptor subtypes, it is the M_3 receptor that primarily controls airway smooth muscle contraction on release of acetylcholine from peripheral parasympathetic nerves. In the search of new improved inhaled muscarinic antagonists, Dr. Jorge Beleta (Laboratories Almirall S.A., Barcelona, Spain) presented on the design of **aclidinium bromide** and its recent phase II clinical data.

In addition to the M_3 receptor, airways also contain a significant M_2 receptor component, blockade of which enhances vagal acetylcholine outflow. Although from binding studies aclidinium bromide shows a level of potency for the M_3 receptor akin to tiotropium bromide, little selectivity is

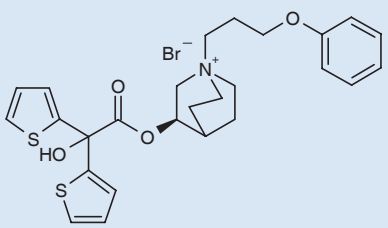


(4)

observed between M_3/M_2 receptors. However, dissociation from the M_3 receptor is much slower compared to the M_2 receptor, giving rise to significant selectivity through kinetic discrimination.

To limit systemic exposure and reduce associated muscarinic side effects after inhalation, the ester group of aclidinium bromide was designed to undergo rapid hydrolysis in human plasma to inactive metabolites. Quinuclidine quaternization in conjunction with optimization of the ester moiety proved key elements in achieving rapid degradation. The soft drug approach for aclidinium bromide may provide improved tolerability over current anticholinergics that remain in plasma. Quaternization also provided a further benefit in preventing undesirable CNS penetration and contributing to delivering a rapid and sustained 24-h duration of action.

Results of a phase II trial in COPD patients receiving escalating doses of aclidinium bromide showed significant increases in FEV_1, compared to placebo, with bronchodilation rapid and sustained at 24 h. Blood samples collected after drug administration revealed no evidence for parent drug or its metabolites. Commercialization of aclidinium bromide is in partnership with Forest Laboratories, with completion of phase III studies expected mid-2008.



Aclidinium bromide

Conclusions

Respiratory diseases present unique challenges and opportunities. In terms of challenges, several poorly treated diseases still remain in need of new therapy. However, it is encouraging, with several different classes of drugs in clinical trials, in particular late stage, that significant progress towards this goal is being made.

By understanding the science behind delivery devices and optimization of direct administration to the airways, coupled with knowledge of achieving rapid onset and long duration of action, inhaled once a day drugs may become more common place in future years within the management of respiratory diseases. A further attractive opportunity of targeting topical delivery resides in drug design, where by rapid elimination of the parent drug from the systemic circulation, or inactivation in plasma via a soft drug approach, has the potential to minimize unwanted systemic effects. However, while high systemic clearance can be used to minimize systemic exposure, in combination with inevitably good permeability through the lung, this can also help drive removal of free drug from the lung. So a continuing challenge for topical treatments is the design of lung retained therapies.

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