

α1 Alpha One
Foundation

ANNUAL REPORT 2015

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MISSION STATEMENT

The Alpha One Foundation is a charity dedicated to raising awareness, increasing diagnosis, promoting research, and improving the treatment of Alpha-1 Antitrypsin Deficiency (Alpha-1).

CORE ACTIVITIES OF THE ALPHA ONE FOUNDATION



STAFF OF THE ALPHA ONE FOUNDATION

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Alpha One Foundation (Ireland) Charity Code: CHY14812



Alpha One Foundation Annual Report 2015

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1. Executive Summary

This year the Alpha One Foundation continued its goal to increase the awareness and detection of Alpha-1 Antitrypsin Deficiency. The National Alpha-1 Targeted Detection Programme received samples from over 32 hospital laboratories, GP practices, and family members of known Alphas. Since 2004 we have screened over 14,000 individuals for Alpha-1. Our centre was visited by Minister for Health Leo Varadkar, T.D. in December 2014, to learn more about Alpha-1 screening and to meet with staff and Alpha-1 patients.

The 5th Global Alpha-1 Patient Congress took place in Barga, Italy early in 2015. Over 200 people from 26 countries attended and this included 3 Irish delegates. Speakers included renowned Alpha-1 scientists and clinicians, as well as industry partners, patients, caregivers and families. By all accounts this was a very successful congress. In July 2015, findings from CSL Behring's RAPID study were published; this demonstrated the effectiveness of replacement therapy in slowing down emphysema due to Alpha-1. This is encouraging news as 23 Irish patients took part in this study. Later in the year CSL received approval for Respreeza (Replacement Therapy) in the European Union. The official opening by Minister for Health Leo Varadkar, T.D. of the new National Rare Disease Office in the Mater Hospital took place in June. This is a very exciting development for people with rare conditions like Alpha-1. As well as providing reliable and accurate information on rare diseases, this office will identify designated centres of excellence for various conditions.

In August a Donegal family launched a book of poetry in memory of their brother John O'Donnell (RIP) who had Alpha-1. The inspiring book of poems written by their brother is called "Window to my World". The launch was attended by over 400 people and locally there was great media interest. An episode of "The Science Squad" a series dedicated to scientific and medical research highlighted Alpha-1, this was broadcast on RTE in October 2014 and repeated in September 2015 and is available to watch on our website. We are grateful to the patients who gave time to be interviewed on the show. Finally, a research study in conjunction with Dublin City University and the Alpha One Foundation will set up a pulmonary Rehabilitation Programme specifically for people with Alpha-1. The programme will be launched at the Annual Alpha-1 Conference this year. We are delighted that this project has been awarded a grant from the Irish Research Council.

Throughout the year other awareness activities included presentations at the Irish Thoracic Society (ITS) conference in Galway, ANÁIL's respiratory nurse conference in Dublin, UCD School of Medicine, COPD Support Groups in Sligo and Mayo, as well as presentations to respiratory and laboratory teams in Peamount, Kilkenny, James Connolly, Mater, Newry, Crumlin Clinical Genetics and Drogheda hospitals. Our annual Alpha-1 conference was held in October 2014 in Marino Institute of Education. This was the best attended conference to date; this provided an excellent opportunity for Alpha-1 patients and family members to meet other Alphas in a relaxed and informal environment. We were especially delighted to welcome John Walsh, CEO Alpha-1 Foundation in the USA to open the conference.

The Alpha One Foundation has continued to work with the Medical Research Charities Group (MRCG), the Irish Donor Network, Irish Platform for Patient Organisations, Science and Industry (IPPOSI), the Irish Lung Health Alliance, the European Organisation for Rare Diseases (EURORDIS) and COPD Support Ireland.

We are very thankful to everyone involved in fundraising in the last 12 months. The efforts have been amazing and varied, mini-marathons, full marathons, table quizzes, poetry book launches, coffee mornings and Christmas cards. The money raised has been used in our national Alpha-1 screening programme.

Hopefully this brief synopsis gives the reader an idea of the progress made by the Alpha One Foundation over the past 12 months. This work is a team effort and I wish to thank all my colleagues for their hard work and dedication throughout the year, particularly Dr. Tomás Carroll and Laura Fee.

Kitty O'Connor,
CEO, Alpha One Foundation

2. An Update from the National Alpha-1 Antitrypsin Deficiency Targeted Detection Programme

WHO SHOULD BE TESTED FOR ALPHA-1?

World Health Organisation (WHO), American Thoracic Society (ATS), and European Respiratory Society (ERS) guidelines advocate targeted detection programmes for alpha-1 antitrypsin deficiency (Alpha-1 for short). These guidelines recommend targeted testing of patients with chronic obstructive pulmonary disease (COPD), severe non-responsive asthma, cryptogenic (unexplained) liver disease and first-degree relatives of individuals with Alpha-1 (Table 2.1).

TABLE 2.1. *ATS/ERS recommendations for diagnostic testing for Alpha-1 (type A recommendations).*

Who Should Be Tested?
Adults with symptomatic emphysema or COPD (regardless of age or smoking history)
Adults with asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators
Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (e.g. cigarette smoking, occupational exposure)
Adults with necrotising panniculitis
Siblings of individuals with Alpha-1
Individuals with unexplained liver disease, including neonates, children, and adults, particularly the elderly

Alpha-1 can be diagnosed by a simple blood test, but sadly it remains under-diagnosed in Ireland and worldwide. A diagnosis of Alpha-1 gives the doctor a unique opportunity for early medical intervention and in some cases the prevention of lung disease in both the affected individual and first-degree relatives. Unfortunately, despite huge advances in awareness and understanding of this condition, this opportunity is often missed. In May 2004, a national targeted detection programme for Alpha-1 was launched by the Alpha One Foundation, based at the RCSI Education and Research Centre at Beaumont Hospital.

HOW DO WE TEST FOR ALPHA-1?

There are two tests needed to correctly diagnose Alpha-1. The first test measures how much alpha-1 antitrypsin (or AAT) is in the blood. If this result is low, the second test looks at what type of alpha-1 antitrypsin is present (phenotyping).

The measurement of alpha-1 antitrypsin is carried out in collaboration with Dr Bill Tormey, Pat O'Brien, and Emma Pentony of the Department of Chemical Pathology in Beaumont Hospital. Quantification is performed by immune

turbidimetry on the Olympus AU4500 instrument. The Department of Chemical Pathology has attained INAB accreditation which means all tests are performed to the highest standards.

To look at the type of alpha-1 antitrypsin, we use a technique called isoelectric focusing. This method identifies variants of alpha-1 antitrypsin circulating in human blood, and is known as phenotyping (Figure 2.1). It is the most accurate method of testing for Alpha-1 and identifies not only the most common but also rare AAT variants. From a quality point of view, we have been participating in the UKNEQAS quality assurance scheme for AAT phenotyping since 2007, achieving 100% compliance to date.

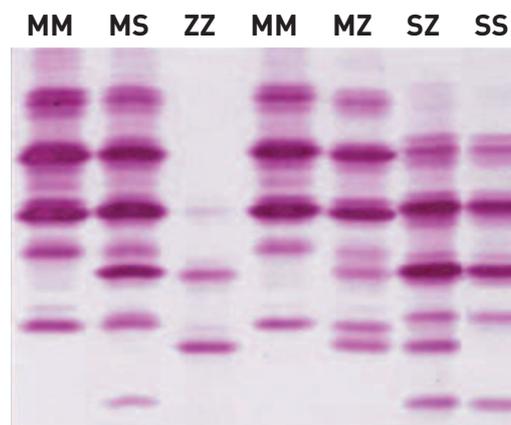


FIGURE 2.1. *Typical isoelectric focusing gel for AAT phenotype identification with the most common phenotypes included.*

WHAT HAVE WE FOUND IN IRELAND?

Since 2004 over 14,500 individuals with COPD, asthma, and liver disease, as well as first-degree relatives of known Alpha-1 individuals have been tested in the national Alpha-1 targeted detection programme. We receive blood samples from over 30 hospitals in Ireland as well as directly from GPs.

A total of 259 ZZ (severe Alpha-1) individuals have been identified, as well as 199 SZ (moderate Alpha-1) individuals, who are also at risk of developing lung and liver disease (Figure 2.2). In addition, a large number of other clinically significant phenotypes have been detected including 2,067 MZ, 74 SS, 19 IZ, and 10 IS phenotypes. The percentage of deficiency alleles (approximately 30%) detected has been quite high, even allowing for the targeted nature of screening. A number of rare AAT mutations have also been identified, including I, F, M_{wurzburg}, Z_{bristol}, M_{malton} and three different Null mutations (Null_{bolton}, Null_{cork}, and Null_{dublin}).

FIGURE 2.2. Alpha-1 phenotypes identified in National Targeted Detection Programme

Dublin	Requests
St Vincent's University Hospital	2412
Beaumont Hospital	2327
Bon Secours Dublin	690
St James's Hospital	586
Connolly Hospital Blanchardstown	568
Peamount Hospital	257
Our Lady's Children's Hospital, Crumlin	199
The Adelaide & Meath Hospital, Dublin	150
Mater Misericordiae University Hospital	139
Temple St Children's University Hospital	53
Coombe Hospital	22
St Columcille's Hospital	14
Rotunda Hospital Dublin	10
Blackrock Clinic	9
Mount Carmel Hospital	3
National Maternity Hospital, Holles St	1

TABLE 2.3. Requests from hospitals nationwide (excluding Dublin).

Nationwide	Requests
Sligo General Hospital	1105
Letterkenny General Hospital	1067
Cork University Hospitals	1047
Cavan General Hospital	750
Bon Secours Tralee	422
Naas General Hospital	374
Galway University Hospitals	326
Midland Regional Hospital Mullingar	199
Mid-Western Regional Hospital Limerick	182
Our Lady of Lourdes Hospital Drogheda	142
University Hospital Waterford	139
Midland Regional Hospital Tullamore	90
Roscommon County Hospital	89
Mayo General Hospital	18
Kerry General Hospital	11
Midland Regional Hospital Portlaoise	10
Monaghan General Hospital	8
Louth County Hospital	3
Navan Hospital	3
Clane General Hospital	1
Bon Secours Galway	1

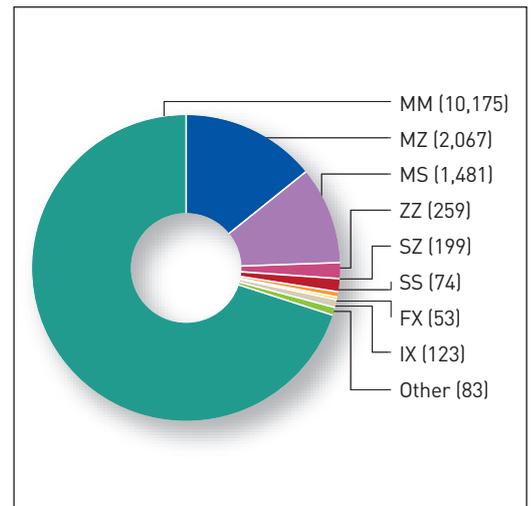


TABLE 2.2. Requests from Dublin area hospitals.

The primary reason for the screening programme is to ensure people with Alpha-1 get correctly diagnosed, and to provide the opportunity to receive specialist and timely care. Newly diagnosed individuals can be referred to our dedicated Alpha-1 clinic in Beaumont Hospital under the care of Professor Gerry McElvaney. In addition, family screening allows the identification of younger relatives with Alpha-1. These individuals benefit from lifestyle changes such as smoking cessation and closer medical observation which can help prevent or postpone the development of lung disease.

In the past 12 months we have presented results from our screening programme to the respiratory and biochemistry departments in Mater, Blanchardstown, Crumlin, and Peamount hospitals in Dublin, as well as Drogheda, Newry, and Kilkenny hospitals. The main aim of these presentations is to increase awareness of Alpha-1 amongst the respiratory and paramedical community. While the respiratory (and liver) teams are dealing with patient populations most at risk due to Alpha-1, many hospital Immunology, Biochemistry, and Clinical Chemistry Departments measure alpha-1 antitrypsin levels as a routine test during normal blood investigations.

Furthermore, in an excellent example of joined-up thinking 9 laboratories have adopted a "red flag" system for AAT testing. This system means that if AAT concentrations are measured by a laboratory and found to be below 1.0 g/L, an automatic "red flag" is included on the laboratory report to recommend testing for Alpha-1. This 1.0 g/L value was found to achieve the greatest sensitivity, specificity, and cost-efficiency in the detection of Alpha-1 in a large US study (Donato LJ et al. 2012). It is hoped that an electronic prompt system will lead to earlier diagnosis of Alpha-1 cases. The ultimate goal would be the adoption of this red flag system on AAT lab reports in every hospital in Ireland.

3. The National Alpha-1 Antitrypsin Deficiency Registry

The National Alpha-1 Registry is a secure, confidential registry that records medical information from individuals with alpha-1 antitrypsin deficiency. This database stores valuable clinical information such as lung and liver test results, smoking history, radiology results, and symptom details which improves our understanding of the condition, facilitates clinical research, and helps in the design of clinical trials. In order to be included in the registry a person must give their written informed consent after first reading an information leaflet about the registry. Participation in the registry is voluntary.

There are currently 280 Alpha-1 individuals from 30 counties in Ireland included on the registry. The process is ongoing and we hope to include as many Alpha-1 individuals attending the national Alpha-1 clinic as possible.

If you have any questions relating to the National Alpha-1 Registry please contact:

Laura Fee, Clinical Research Associate, Alpha One Suite, Beaumont Hospital, Dublin 9.
Telephone: 01-8093702. Email: alpha1@rcsi.ie

FIGURE 3.1. Total number of ZZ Alpha-1 cases detected per county.

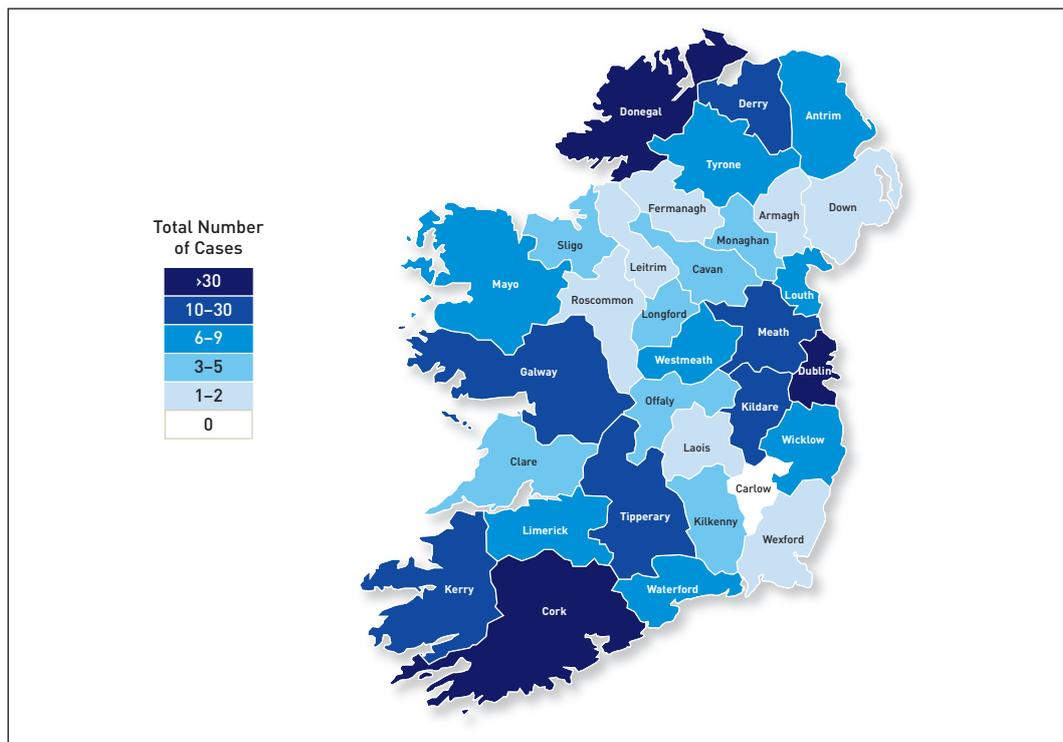
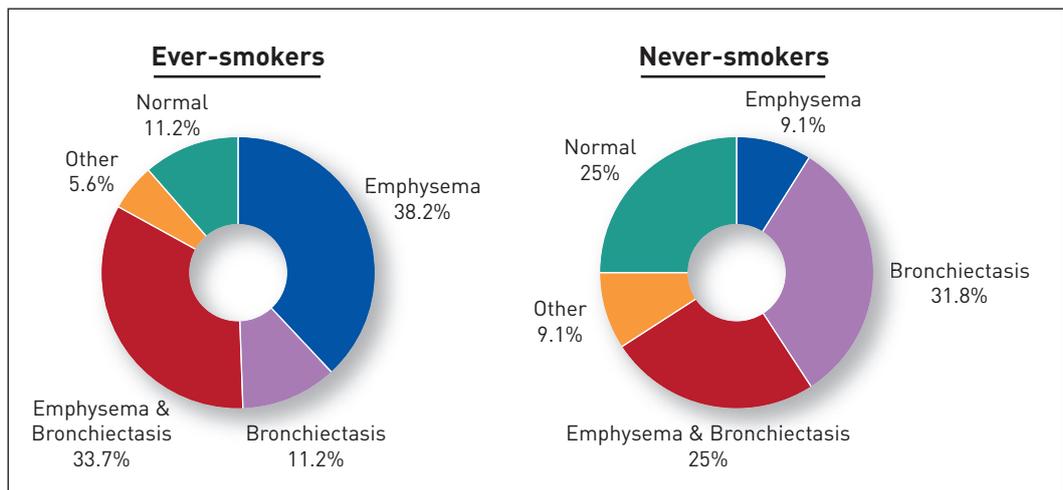


FIGURE 3.2. CT Findings in ever-smoking (current/past smoker) and never-smoking ZZ individuals on the National Alpha-1 Registry.



4. Current Research Developments in Alpha-1

RESEARCH STUDIES

Earlier this year RCSI researchers in Beaumont Hospital teamed up with the Alpha One Foundation to assess the impact of cigarette smoke on the development of lung disease in Alpha-1. Data was collected using an anonymous questionnaire either posted out or provided in the Alpha-1 clinic. Study results published in the Journal of COPD confirmed the harmful effects of smoke exposure in Alpha-1, and also demonstrated that children with Alpha-1 exposed to passive smoke are more likely to take up smoking, placing this vulnerable group at increased risk for the development of lung disease. For people with Alpha-1, this study highlights the need to avoid smoking uptake, promote smoking cessation and reduce passive smoke exposure.

Over the last 12 months RCSI researchers made two important breakthroughs in Alpha-1. The first study was published in the Journal of Immunology and showed how the alpha-1 protein plays an important role in controlling inflammation caused by a fat-molecule called leukotriene B₄ (LTB₄). It was revealed just how amazing the alpha-1 protein is, as it was shown to have a small pocket on its surface that can bind LTB₄ and prevent the fat-molecule from speaking to white blood cells. The second study demonstrated how Alpha-1 increases the life-span of white blood cells and improves the bacterial killing ability of these important immune cells.

A new research study in RCSI Beaumont Hospital is looking at "augmentation therapy" which involves boosting the levels of the alpha-1 protein in patients. In new pilot research we will examine whether "microRNAs" play a role in the beneficial effects of augmentation therapy. microRNAs are molecules present in every cell in the body that have important roles in maintaining normal cell function. Our experiments using cells isolated from people with and without Alpha-1 will examine microRNAs, and data generated will provide new insight into how "augmentation therapy" works. Funding for current research projects is gratefully acknowledged from the HRB/MRCG joint funding scheme and the US Alpha-1 Foundation.

This research is being carried out by a dynamic team in the Department of Medicine in RCSI including scientists, doctors and nurses under the leadership of Professor McElvaney. These research projects give a greater understanding of Alpha-1 and allow us to develop new therapies, design better clinical trials, improve

the care of patients, and ultimately lead to better health outcomes for Alpha-1 patients.



Department of Medicine, Respiratory Research team based in the RCSI Education and Research Centre, Beaumont Hospital.

CLINICAL TRIALS - RAPID STUDY

The **RAPID study** was a multicentre, double blind, randomised, placebo-controlled phase III/IV trial of alpha-1 antitrypsin replacement therapy (called Zemaira) in patients with Alpha-1 sponsored by CSL Behring. The aim of the trial was to assess the safety and efficacy of Zemaira® given intravenously to patients with emphysema due to Alpha-1. A total of 180 Alpha-1 patients across 28 sites in the USA, Europe, Canada, Australia and Russia were randomly assigned either Zemaira or a placebo for a two year period, followed by an open-label extension study in which all participants were offered augmentation therapy for the following two years. Twenty-four patients were enrolled at the RCSI Clinical Research Centre in Beaumont Hospital.

The RAPID study is the first well-powered randomised, placebo-controlled trial using CT scan lung density as the primary outcome measure with CT scan lung density measured at baseline, three months, one and two years during the study. CT scans are considered to be the most sensitive measure of emphysema progression. Other endpoints included spirometry, changes in exercise capacity and the rate of pulmonary exacerbations over the two year period.

The annual rate of lung density loss was significantly less in augmentation-treated patients compared to those receiving placebo. Secondary outcomes and adverse events were not significantly different between groups. In addition, when patients initially receiving placebo began augmentation therapy on the open-label extension study their lung density decline (which was more rapid during the first two years) slowed to the same rate as the treatment group.

5. New Exercise Programme for Alpha-1

ARE YOU INTERESTED IN TAKING PART IN A RESEARCH STUDY LOOKING AT EXERCISE AS A THERAPY FOR ALPHA-1?

In collaboration with Dublin City University Sport (DCU Sport) and MedEx Wellness, the Alpha One Foundation is delighted to announce an exciting new research project which is being funded by the Irish Research Council. Bringing together a wealth of experience in the fields of pulmonary rehabilitation and exercise physiology our goal is to find out how physically active people with Alpha-1 are. This information will then be used to design a home based exercise programme specifically tailored to the needs of people living with Alpha-1.

The many benefits of regular exercise apply in particular to those with Alpha-1. Research has shown that regular physical activity can greatly enhance the management and treatment of many chronic conditions, including the lung problems often associated with Alpha-1. In addition exercise can improve the health of your heart, aid weight loss, decrease exacerbations (infections) and improve quality of life and general wellbeing. From December we hope to offer medically supervised exercise classes in DCU Sport to Alpha-1 patients.

The exercise classes will take place in DCU and are being run by MedEx Wellness. Founded in 2006, MedEx Wellness is a unique partnership between DCU Sport, the School of Health and Human Performance and local health care providers. It offers medically supervised group

exercise classes involving a mixture of aerobic and resistance training in a relaxed, friendly and supportive environment. All staff are highly trained and experienced in helping people with chronic illnesses to exercise safely and become fitter, healthier and better able to enjoy an active lifestyle.

We require participants of all ages and with different forms of Alpha-1 to take part. You do not need to have any lung disease; all we ask is that you commit to attending DCU on two separate occasions for a series of tests, including a walk test and some tests of your lung function. Following completion of these tests, we will invite you to attend the supervised exercise classes in DCU. The decision to attend is entirely yours and may be based on where you live and how convenient it is for you to travel to DCU twice a week. If you do not live close to DCU, we would still like to hear from you. Our ultimate goal is to design a home programme for people with Alpha-1 and we need participants who are based outside of North Dublin so we can measure their physical activity levels during their daily lives. We then hope to retest all participants after 6 and 12 weeks to see if there is any improvement in your health and fitness following the exercise classes. We are also looking for individuals without Alpha-1, but who may have chronic obstructive pulmonary disease or COPD to take part.

If you would like to know more or are interested in taking part, please contact Eóin Durkan at eoin.durkan@dcu.ie or call 01 7008470.

Left to Right: Prof. Niall Moyna, Head of School of Health and Human Performance, DCU, Eóin Durkan, PhD Researcher, DCU. Dr. Noel McCaffrey, Medical Director MedEx Wellness, Kitty O'Connor, CEO Alpha One Foundation, and Dr. Tomás Carroll, Chief Scientist Alpha One Foundation.



6. Alpha-1 and Panniculitis

Panniculitis is an inflammation of the panniculus, the layer of fatty and fibrous tissue beneath the skin. This inflammation can cause the skin to harden and form painful lumps, patches or lesions. This damage is started by an excess of white blood cells and the substances they release.

Panniculitis can have many underlying causes including diseases that involve widespread inflammation of the body (e.g. lupus and rheumatoid arthritis), reactions to some drugs such as corticosteroids, and **alpha-1 antitrypsin deficiency** (Alpha-1). Guidelines from leading respiratory societies recommend doctors to test for Alpha-1 in patients with panniculitis.

TABLE 6.1. ATS/ERS recommendations for diagnostic testing for Alpha-1 (type A recommendations)

Who Should Be Tested for Alpha-1?	
✓	Adults with symptomatic emphysema or COPD (regardless of age or smoking history)
✓	Adults with asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators
✓	Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (e.g. cigarette smoking, occupational exposure)
✓	Adults with necrotising panniculitis
✓	Siblings of individuals with Alpha-1
✓	Individuals with unexplained liver disease, including neonates, children, and adults, particularly the elderly

Panniculitis typically appears as raised red spots on the skin which may break down and give off an oily discharge. These raised spots (nodules) can appear anywhere on the body but the most common places are the thighs, buttocks and areas subject to pressure and/or injury. This includes injury that would be minor in most people e.g. vigorous exercise, intravenous injections and cryosurgery (surgery which involves freezing the skin). Diagnosis is made by skin biopsy. Panniculitis seems to occur equally among men and women and has been reported in all age groups however the mean age of onset is about 40 years old.

Panniculitis in Alpha-1 is not limited to particular phenotypes. It can be found in those with severe deficiency of alpha-1 antitrypsin (e.g. ZZ) and also in those with a milder deficiency (e.g. SZ and MZ). Panniculitis is one of the rarest of the complications of Alpha-1, but it may be under-reported. If you have been diagnosed with Alpha-1 and you notice any suspicious rashes anywhere on your skin, you should mention this to your GP or at your next outpatient appointment.

Various therapies are used to treat panniculitis, including panniculitis due to Alpha-1. These include corticosteroids, antibiotics and augmentation therapy (intravenous infusions of plasma-purified alpha-1 antitrypsin protein. In panniculitis caused by Alpha-1, augmentation therapy has been found to be the most successful therapy.

A case report describing panniculitis in an Irish Alpha-1 patient was published recently in the prestigious American journal *Chest*, a shortened version of which appears in the next section.

UNUSUAL ACUTE SEQUELAE OF ALPHA-1 ANTITRYPSIN DEFICIENCY (AATD): A MYRIAD OF SYMPTOMS WITH ONE COMMON CURE (FRANCIOSI, MCCARTHY ET AL., CHEST, 2015).

Case Report

A 23 year old male with ZZ AATD diagnosed at nine months secondary to acute hepatitis, presented with an acutely swollen right knee. Investigation revealed a joint effusion with a predominantly neutrophilic cell count. Fluid analysis ruled out septic arthritis. Reactive arthritis was diagnosed and the patient was discharged on non-steroidal anti-inflammatory medication; however he reported a slow response to this treatment.

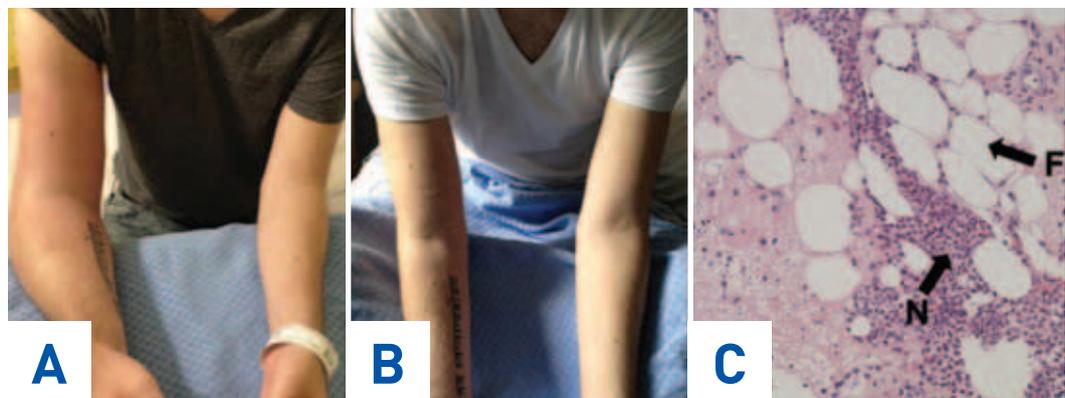
Eight weeks later, the same patient presented to a different institution with chest pain and breathlessness. Chest-radiograph revealed large bilateral effusions. Pleural fluid analysis revealed a neutrophilic low pH exudate and no organisms were cultured. Chest drains were inserted and broad-spectrum antibiotics were commenced. Inflammatory markers remained persistently elevated despite broad spectrum antimicrobials. Pleural fluid drainage persisted and the patient was admitted to intensive care for management of progressive respiratory failure. Following consultation with the national AATD referral centre in Beaumont Hospital, a single dose of 120mg/kg of plasma purified AAT was administered intravenously. The patient showed remarkable clinical recovery within 24 hours, his respiratory failure completely resolved, inflammatory markers normalized, and pleural effusions resolved entirely with chest drains being removed 48 hours after administration of plasma purified AAT. The patient was discharged one week later.

Six weeks later he presented to our institution with a diffusely swollen, tender right upper arm and forearm, associated with subcutaneous induration and a 5cm difference in upper limb circumference (Figure 6.1A). No convincing evidence for an infectious cause was identified and there was no evidence of deep vein thrombosis on venous duplex and inflammatory markers were raised. No anti-microbial or anti-inflammatory medications were administered. Punch-biopsy of the indurated area revealed extensive panniculitis with neutrophils, foamy macrophages and fat necrosis, confirming a diagnosis of AATD-associated panniculitis (Figure 6.1C). Following this a single dose of 120mg/kg of plasma purified AAT was administered. By day seven post AAT infusion inflammatory markers had normalized and limb circumference difference was 1cm. There was no tenderness to palpation or induration and a clinical remission of panniculitis was observed (Figure 6.1B).

Discussion

Several previous case reports have shown a response to serial doses of AAT augmentation in AATD associated polyserositis/panniculitis with some cases reporting dramatic clinical response to augmentation after as little as 3 doses. However, we report the first case of complete clinical resolution following a single dose of plasma purified AAT in two distinct clinical presentations, polyserositis and panniculitis.

FIGURE 6.1. PANEL A: Diffusely swollen and erythematous right upper limb pre-treatment with intravenous plasma-purified AAT. **Panel B:** Resolution of swelling and inflammation of right upper limb one week after administration of plasma-purified AAT. **Panel C:** Skin biopsy showing neutrophilic inflammation (N), foamy macrophages and fat necrosis (F) confirming panniculitis.



7. Recent Events

President and CEO of the US Alpha-1 Foundation John Walsh speaking at the Alpha-1 Patient Conference



ANNUAL ALPHA-1 PATIENT CONFERENCE OCTOBER 2014

The annual Alpha-1 patient conference took place once again in the Marino Institute of Education in Dublin in October 2014. Over 50 Alphas and members of their families attended on the day making it one of the biggest patient meetings to date. We were delighted to have President and CEO of the US Alpha-1 Foundation John Walsh who spoke about his own history of Alpha-1, the Alpha-1 Foundation in the US and its ongoing links with Ireland. Other speakers included Professor McElvaney who spoke on clinical research carried out on Alpha-1 to date, Dr Kevin Molloy and Dr Emer Reeves both from the Department of Medicine, RCSI, Damien Peelo, CEO of COPD Support Ireland and Michelle O'Brien senior physiotherapist in St Michael's Hospital in Dún Laoghaire. The Alpha-1 support group presented a cheque of €2,000 to the Alpha One Foundation on the day which went towards a much needed upgrade of our IT system and website.

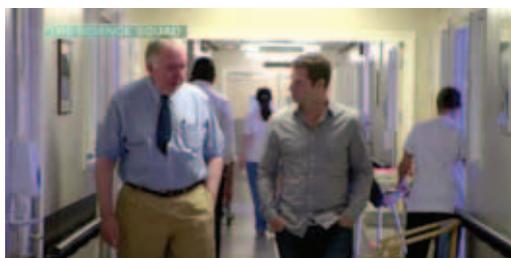
Minister for Health Leo Varadkar meeting members of the Alpha One Foundation and Alpha-1 patient Josephine McGuirk



LEO VARADKAR VISIT DECEMBER 2014

Minister for Health Leo Varadkar visited the Alpha One Foundation in December 2014. During the Minister's visit Professor McElvaney spoke about the national screening programme and the services provided by the Alpha One Foundation with the Minister expressing surprise at the high prevalence of Alpha-1 in Ireland. Minister Varadkar was also given a tour of the facilities and spoke with Mrs Josephine McGuirk who was diagnosed with Alpha-1 15 years ago following her brother's diagnosis.

Professor McElvaney speaking on the Science Squad



SCIENCE SQUAD DECEMBER 2014

Alpha-1 featured on an episode of RTE's The Science Squad in December 2014. The episode featured an interview with Professor McElvaney and two inspirational Alpha-1 patient stories from Stephen Smith and Josephine McGuirk. This episode was an excellent opportunity to help spread awareness of Alpha-1 nationally.

Alpha-1 Global Patient Congress, Barga



5TH ALPHA-1 GLOBAL PATIENT CONGRESS IN BARGA, ITALY. APRIL 2015

The 5th International Alpha-1 Patient Conference and 2nd Biennial International Research Conference on Alpha-1 took place in Barga Italy in April 2015. Three Irish delegates and their families travelled over. See section 8 for a full report on the event.

Minister for Health Leo Varadkar speaking at the opening of the National Rare Disease Office in the Mater Hospital



NATIONAL RARE DISEASE OFFICE OPENING, JUNE 2015

The new National Rare Disease Office was opened in June 2014 by Minister for Health Leo Varadkar in the Mater Hospital, Dublin. The principal functions of the office will include the development of a database of expertise in rare diseases, the set up of a helpline function for patients and clinicians, and providing the locations of medical experts and of research and genetic testing in rare diseases.

Dr Tomás Carroll presenting at the Waterford COPD Support group



COPD SUPPORT MEETINGS

Tomás Carroll of the Alpha One Foundation presented at both the Waterford COPD Support Group, Benbulbin COPD Support Group (Sligo) and Mayo COPD Support Group in the last twelve months speaking about Alpha-1 and the work of the Alpha One Foundation. This is helping to raise awareness of Alpha-1 among the general COPD population and we hope to attend more in the coming year.

FUNDRAISING

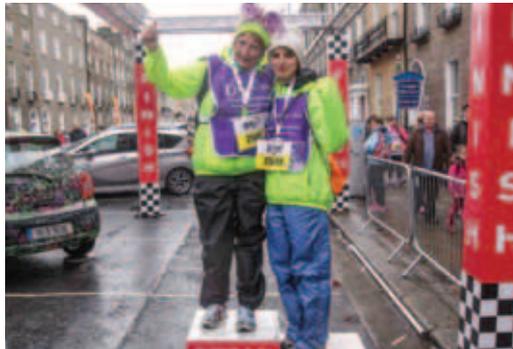
Alpha One Foundation Christmas Cards 2015

We had yet another successful year with our Christmas cards this year. Many thanks to all who bought these and shared with family and friends. We will have cards on sale again this year, please contact us on 01 809 3871 or check our website for more details.



Ladies Mini Marathons, Cork + Dublin

Right: Orla and Mary Keane after completing the VHI Women's Mini Marathon in Dublin, June 2015



Far right: Annette Rundgren following the Cork Mini Marathon, September 2014



Alpha-1 Coffee Morning, Maynooth

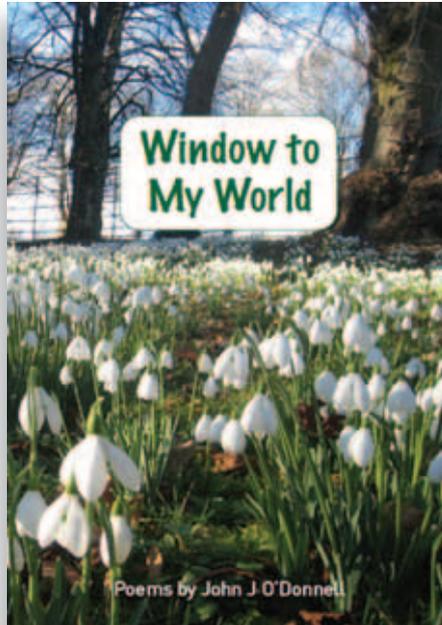
Orla Keane and friends at coffee morning in aid of Alpha-1 in Maynooth, June 2015



Drumalee GFC Over 35s

Stephen Smith with his local GAA club Drumalee GFC (Cavan), and their Over 35s team who participated in a charity tournament in June 2015





WINDOW TO MY WORLD BOOK LAUNCH

A Donegal family recently launched a book of poetry in memory of their brother who had Alpha-1. The book of poems called 'Window to my World' was written by their brother John O'Donnell who passed away in 1987 aged 26. The launch took place in August in the Resource Centre in Manorcunningham, Co. Donegal with over 400 people attending and was covered in local media and radio. The O'Donnell family also organised a fundraising day in their local Bank of Ireland. Proceeds from the sale of the book will go towards the Alpha One Foundation. Congratulations and well done to all involved.



A BIG THANK YOU!

The Alpha One Foundation wish to thank all Alpha-1 patients and family members who have helped with fundraising and been involved in events throughout the year. If you wish to get involved in the coming year contact us at **01-809 3871** or **alpha1@rcsi.ie**.

8. Fifth Alpha-1 Global Patient Congress

The 5th Alpha-1 Global Patient Congress was held from April 9th to 11th in the medieval town of Barga in the Tuscany region of Italy. Over 200 people from 26 countries heard renowned Alpha-1 scientists, clinicians, experts, industry partners, patients, caregivers and family speak on the status of the latest research, the regulatory framework for licensing therapies for rare disease in Europe, the status of patient

registries and ways to strengthen the Alpha-1 message globally. The Congress was the first organised by Alpha-1 Global, a programme of the US Alpha-1 Foundation dedicated to building a collaborative network of organisations for patients and their families worldwide. Three Irish delegates and their families attended representing Irish Alphas and the Alpha One Foundation of Ireland.



Harry and Mary Pat English

HARRY ENGLISH

We arrived at the Renaissance hotel at around 7.30pm on Thursday evening, just as the reception was finishing; unfortunately, our flight was delayed so we went straight to dinner. We sat with our two fellow Irish, Michael and Philomena, along with two ladies from Sweden and one from Brazil. The two Swedish ladies had both received transplants just like myself and the Brazilian lady had a young daughter with Alpha-1. From the chat in the room, you would think everybody knew each other all of their lives. The next couple of days, we met people from all over the world and they all had their own stories to share about Alpha-1.

The conference itself was very interesting, with different speakers talking about different aspects of Alpha-1, such as augmentation therapy, transplantation, gene and stem therapy and in the future, inhaler therapy instead of transfusion therapy. So the future is looking positive for us Alphas.

When talking to other Alphas from different countries, I realised how lucky we are to live here in Ireland as we are getting the best treatment possible. We have such a great medical team looking after us and the fact that we are such a small country, we are never more than a couple of hours from medical assistance or indeed from getting invaluable information and support by attending one of the Alpha-1 conferences. From talking to people from countries like Canada or Australia, they might have to take a six hour flight to attend a conference or to attain medical care, so you are talking about spending a couple of days away from home.

Also, a lot of these countries have no augmentation therapy yet, so it was a very interesting and enjoyable four days and we were delighted to be invited to it.

Michelle Monaghan

I am a parent of a ZZ Alpha, Ben, who is now 12 years old. For about 8 years all we knew was information from our doctors at appointments. We had never met another alpha, nor a parent of one. We then got invited to the Dublin Alpha-1 patient conference which was a wealth of knowledge each time we went. From here we got the amazing opportunity to go to the global conference in Italy. I discovered how other countries deal with Alpha-1, from genetic discrimination and raising awareness to treatments available in each country.

Alpha-1 was discussed in great detail, I had not known a lot about therapies so I feel more secure for the future knowing that there are such great options.

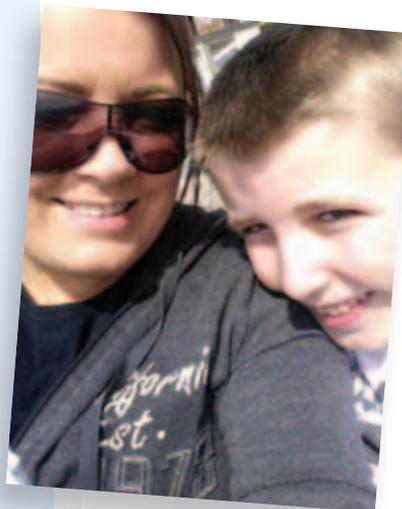
I met the wonderful Jemma Louise Coad who is Parent Support in the UK, who recently had a parent and child meet up in the UK. I would like to think maybe this could be organised in Ireland someday. I have now added myself to the support groups and know now where I can direct questions when they arise.

I also met Bill Clark from the COPD Foundation, and his wife Alice. I think I learned nearly as much from Bill sitting at dinner, he is certainly an inspiration!

From talking to Mimi McPhedran from Canada, I got a great children's alpha-1 book posted to us, much to Bens delight!

Networking at the Alpha-1 global conference was invaluable, and the support groups I've joined since share new information as it arises. I now feel more secure, knowing I have people to talk to and ask questions to.

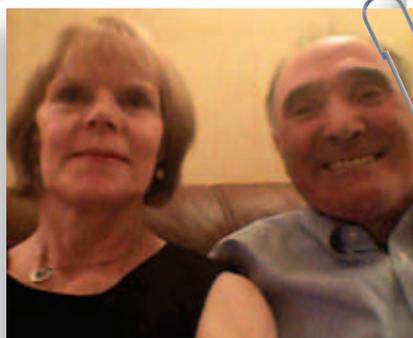
I am forever grateful for the opportunity to attend the global conference.



Michelle and Ben Monaghan

Michael McNamee

I would like to thank the Alpha One Foundation for giving us the opportunity to attend the Alpha-1 Global Conference in Tuscany. We enjoyed our time there and met some wonderful people from lots of different countries. It was great to meet people who have received lung transplants. It was really interesting to hear their stories and to see how it has changed their lives. We have great admiration for all the alpha foundation members who work tirelessly to find new treatments. It was interesting to learn how some countries work together promoting awareness. Their goal is to find a cure and hopefully this will be possible some day.



Philomena and Michael McNamee

9. Acknowledgements

We would like to thank the following:

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 - Pat O'Brien, Emma Pentony, Helen Moore, Dr Bill Tormey and the Beaumont Hospital Chemical Pathology Department for their continued support and advice
 - John Walsh and Angela McBride of the Alpha-1 Foundation (USA) and Gonny Gutierrez of Alpha-1 Global
 - Professor Maurizio Luisetti (RIP), Dr Ilaria Ferrarotti and Dr Stefania Ottaviani, Centre for Diagnosis of Inherited Alpha-1 Antitrypsin Deficiency, University of Pavia, Italy
 - The Health Research Board (HRB), The Medical Research Charities Group (MRCG), and the Irish Platform for Patients' Organisations, Science & Industry (IPPOSI)
 - Dr Paula Byrne and Dr Amanda McCann of the UCD School of Medicine
 - Professor Dermot Kenny and the RCSI Clinical Research Centre (www.rcsicrc.ie)
 - Josephine McGuirk and Stephen Smith for their help in the production of the special piece on Alpha-1 for RTE's The Science Squad
 - Amina Nameera and Zafirah Aqilah Zainal Abidin, 3rd Year Medical Students, RCSI and Bryan Lee, 2nd Year Medical Student, RCSI who carried out research projects with the Alpha One Foundation in 2015.
 - A special thank you to everyone who took part in or organised fundraising events throughout the year.
- Cork University Hospitals
 - Galway University Hospitals
 - James Connolly Memorial Hospital Blanchardstown
 - Kerry General Hospital
 - Letterkenny General Hospital
 - Mater Misericordiae University Hospital, Dublin
 - Mayo General Hospital
 - Midland Regional Hospitals: Tullamore, Mullingar, and Portlaoise
 - Midwestern Regional Hospital, Limerick
 - Naas General Hospital, Co. Kildare
 - Our Lady's Children's Hospital, Crumlin
 - Our Lady of Lourdes Hospital, Drogheda
 - Our Lady's Hospital, Navan
 - Peamount Hospital, Dublin
 - Roscommon County Hospital
 - Rotunda Hospital, Dublin
 - Sligo General Hospital
 - St James's Hospital, Dublin
 - St Luke's General Hospital Carlow/Kilkenny
 - St Vincent's University Hospital, Dublin
 - South Tipperary General Hospital, Clonmel
 - Waterford Regional Hospital
 - Wexford General Hospital

We would also like to thank the Department of Health and Children and the Health Service Executive for their continued financial support.

We would also like to acknowledge the participation of the following hospitals;

- Adelaide and Meath Hospitals, including National Children's Hospital Tallaght
- Beaumont Hospital
- Blackrock Clinic
- Bon Secours Hospital Tralee
- Bon Secours Hospital Dublin
- Cavan General Hospital
- Children's University Hospital, Temple Street, Dublin
- Coombe Women and Infants University Hospital

IN MEMORIAM

Annual Report 2015 is dedicated to the memory of Professor Maurizio Luisetti of the University of Pavia in Italy who passed away suddenly last October. Maurizio was a giant in the field of Alpha-1 and a great friend to the Alpha One Foundation in Ireland. He will be sadly missed. His group in the University of Pavia continue to help us in the diagnosis of rare and novel alpha-1 antitrypsin mutations in Ireland.

Recent Irish Research Publications in Alpha-1

Unusual acute sequelae of Alpha-1 Antitrypsin Deficiency: a myriad of symptoms with one common cure

Franciosi AN, McCarthy C, Carroll TP, McElvaney NG. *Chest*, Oct 2015 (in press).

The BLT1 inhibitory function of alpha-1 antitrypsin augmentation therapy disrupts leukotriene B₄ neutrophil signaling

O'Dwyer CA, O'Brien ME, Wormald MR, White MM, Banville N, Hurley K, McCarthy C, McElvaney NG, Reeves EP. *Journal of Immunology*, 2015 Oct 15;195(8):3628-41. PMID: 26371243.

Intravenous augmentation treatment and lung density in severe α 1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial

Chapman KR, Burdon JG, Piitulainen E, Sandhaus RA, Seersholm N, Stocks JM, Stoel BC, Huang L, Yao Z, Edelman JM, McElvaney NG; RAPID Trial Study Group. *Lancet*. 2015 Jul 25;386(9991):360-8. PMID: 26026936.

The impact of smoke exposure on the clinical phenotype of alpha-1 antitrypsin deficiency in Ireland: exploiting a national registry to understand a rare disease

O'Brien ME, Pennycooke K, Carroll TP, Shum J, Fee LT, O'Connor C, Logan PM, Reeves EP, McElvaney NG. *COPD*. 2015 May;12 Suppl 1:2-9. PMID: 25938284.

Diagnosing α 1-antitrypsin deficiency: how to improve the current algorithm

McElvaney NG. *European Respiratory Review*. 2015 Mar;24(135):52-7. PMID: 25726555.

Alpha-1 proteinase inhibitors for the treatment of alpha-1 antitrypsin deficiency: safety, tolerability, and patient outcomes

Chotirmall SH, Al-Alawi M, McEnery T, McElvaney NG. *Journal of Therapeutics and Clinical Risk Management*. 2015 Jan 29;11:143-51. PMID: 25673994.

The efficacy and safety of inhaled human α -1 antitrypsin in people with α -1 antitrypsin deficiency-related emphysema

Franciosi AN, McCarthy C, McElvaney NG. *Expert Review of Respiratory Medicine*. 2015 Apr;9(2):143-51. PMID: 25598013.

Identification and characterisation of eight novel SERPINA1 Null mutations

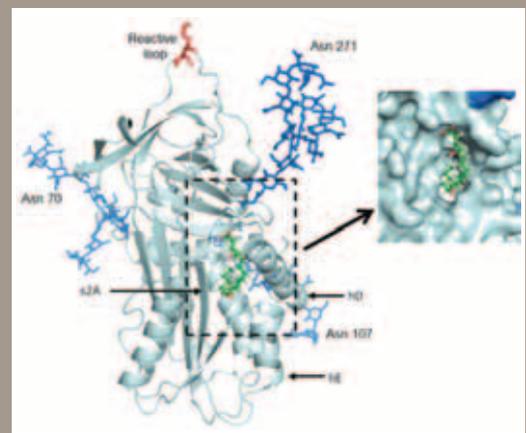
Ferrarotti I, Carroll TP, Ottaviani S, Fra AM, O'Brien G, Molloy K, Corda L, Medicina D, Curran DR, McElvaney NG, Luisetti M. *Orphanet Journal of Rare Diseases*. 2014 Nov 26;9:172. PMID: 25425243.

α 1-Antitrypsin activates protein phosphatase 2A to counter lung inflammatory responses

Geraghty P, Eden E, Pillai M, Campos M, McElvaney NG, Foronjy RF. *American Journal of Respiratory and Critical Care Medicine*. 2014 Dec 1;190(11):1229-42. PMID: 25341065.

Alpha-1 antitrypsin augmentation therapy corrects accelerated neutrophil apoptosis in deficient individuals

Hurley K, Lacey N, O'Dwyer CA, Bergin DA, McElvaney OJ, O'Brien ME, McElvaney OF, Reeves EP, McElvaney NG. *Journal of Immunology*. 2014 Oct 15;193(8):3978-91. PMID: 25217166.



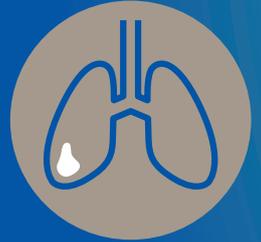
LTB₄ (bright green) shown bound in a pocket of the Alpha-1 protein

From: O'Dwyer et al., *Journal of Immunology*, Oct 2015



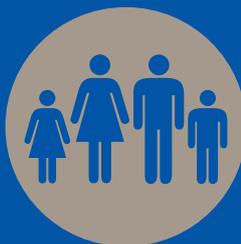
The overall prevalence of cigarette smoking in Ireland is currently **19.5%**

Smokers who carry one defective Alpha-1 gene have a **5 times** increased risk of developing lung disease



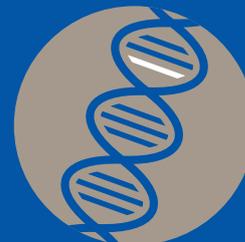
2004 – Irish National Screening Programme for Alpha-1 Antitrypsin Deficiency began

200 blood tests performed by the Alpha One Foundation per month



14,500 individuals tested for Alpha-1 to date

1 in 25 people in Ireland carry the defective Z Alpha-1 gene



>600 attending National Alpha-1 Clinic in Beaumont Hospital

>30 hospitals in Ireland sending samples for Alpha-1 testing



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