The Aplastic Anaemia Trust

Research Strategy
2018-21

1. Foreword

I am delighted to welcome the AAT's first Research Strategy that builds on our solid research foundations and successes, recent breakthroughs in alternative treatment studies, such as cellular therapies, and new clinical trials, leading to much hope for the future of hundreds of patients.

We want to make sure that all investments we make into research makes a difference to everyone affected by a rare bone marrow failure, and especially aplastic anaemia, and gets us closer to a cure.

Research, some of it supported by the Aplastic Anaemia Trust, and led by eminent clinical experts in the UK - at St George's and at King's, has already led to ground-breaking improvements in clinical care, better understanding of the diseases, improved treatments and has resulted in significant impact on the quality and length of life for people affected.

Yet more remains to be done. We need to obtain much better understanding of the disease prevalence in the UK in all populations of patients, to enable new trials of innovative treatments targeted at those individuals who do not respond well to some of the more established drugs, and to highlight to the NHS the extent and unmet needs of this serious condition. We also need to encourage new scientific talent to join clinical teams in haematology, support collaborative scientific working both in the UK and with our international colleagues and share research findings broadly across scientific and patient communities.

Professor Ghulam Mufti, Head of Haematology at King's College Hospital, London, Trustee of the AAT Board

2. Introduction

Our proud history

The Aplastic Anaemia Trust emerged as a charity from a previous incarnation, the Marrow Environment Fund (MEF), and Aplastic Anaemia Patient Support network in the late 90s. The change was designed to highlight the main disease the Charity was formed to help, aplastic anaemia (AA). The MEF was started in 1985 by relatives and friends of patients who had suffered from aplastic anaemia and allied conditions of bone marrow failure, including constitutional or inherited disorders. At that time the outlook for patients was very poor. Bone marrow transplantation had been introduced to Hammersmith Hospital, where the MEF originally directed its efforts under the dedicated leadership of Professor Ted Gordon-Smith, in 1972, but only a minority of AA patients at that time were suitable. An innovative treatment to suppress the immune system, antilymphocyte globulin (ALG), had not long been available and trials of its efficacy were just starting.

Little was understood of the nature of these bone marrow failure syndromes and the MEF was established with the aim of promoting understanding through research and improved patient care. The name was chosen, to emphasise the importance of the marrow environment – the "soil" – to the blood forming stem cells – the "seed" but also the special environment, the sterile isolation rooms, in which the patients had to be treated.

In 1987 Professor Ted moved to St George's Hospital Medical School to set up a specialist unit devoted to the study and treatment of AA and other causes of marrow failure.

Our unwavering focus on research

A key aim of the AAT, over the decades, has been the development of research and treatment in a mutually dependent way. The AAT raised and provided funds for a number of research posts at St George's to help set up the programme, including a number of leading scientists.

With a huge supporter backing and fundraising effort, we provided funds for state of the art equipment for the research team to study the nature and functioning of the damaged AA stem cells and the microenvironment. We funded a special in-patient unit – the Ruth Myles Unit for patients with bone marrow failure, particularly but not exclusively for AA. The Group was joined by Prof Judith Marsh who had worked at Hammersmith Hospital in the original clinical team, and acquired further research skills in Manchester and Canada, at the world-renowned stem cell research establishments.

St George's became the main UK centre for AA with an international reputation thanks to the continued support of the AAT for research, equipment, clinical support staff and finally a complete refurbishment of the day care facilities of the Ruth Myles Unit – to this day operating effectively in the treatment of bone marrow failures. The AAT invested nearly £2m in our work with the St George's team.

Following the retirement of Professor Ted and Professor Marsh's move to King's College Hospital, this became a national centre of excellence for rare bone marrow failure patients.

Our recent research work

In more recent years, the AAT has funded ground-breaking clinical research into acquired AA at King's College Hospital, enabling to predict responses to treatment, published in *Blood 2016.*

We have provided funds for a clinical nurse specialist at King's, to co-ordinate vital care and enable patients to participate in clinical trials with nearly 400 patients supported.

We funded the establishment of aplastic anaemia and bone marrow failures registry, enabling the study of epidemiology and planning services for the future. Nearly 500 patients have been recruited, with different types of bone marrow failure, of whom 43% have acquired AA and with 110 people diagnosed with either severe or very severe AA. A break-through finding emerged of higher than expected incidence of inherited AA. This study has enabled a joined project with the National Institute of Health (NIH), USA, to produce the largest study of inherited heterozygous RTEL1 mutations in patients with AA and MDS, published in *Blood Advances,* in 2017*.* We were the first to show an association between acquired somatic mutations in AA and risk of later developing MDS – reported in the *Blood Journal, 2014*

What's in store in the future?

The bone marrow may fail in a number of ways, both acquired disorders and constitutional and inherited diseases. They are all rare in themselves, but together constitute a significant burden of disease affecting numerous patients, including both children and adults, and their families. The mechanisms by which the bone marrow fails may differ between groups of patients, but the consequences are usually equally devastating.

Despite the advances made over the past decades stem cell transplant remains the only hope of permanent cure for the majority of patients. Most require lifelong care even when the marrow appears to have returned to normal blood production.

The AAT aims to raise more money and use its resources to support ground breaking research and management methods in all types of bone marrow failure as well as its pre-eminence in acquired aplastic anaemia. Such a broadening of our remit will benefit the understanding of individual failure mechanisms and improve the lives of many.

We are in a unique position in small medical charity landscape in that we are the only charity in the UK dedicated solely to research into and support of patients with aplastic anaemia and other rare bone marrow failures nationally. We are also able to enjoy long-established productive working relationships with major centres of excellence providing us with direct access to world-renowned clinicians and experts. Access to this medical and scientific expertise puts us in a strong position to identify areas of

need, support and fund research, and engage with the research community in the UK and internationally.

The Charity will reach out nationally to be as inclusive as possible in the aim of improving patient care wherever it is needed for these rare conditions. Just because a condition is rare does not mean that individuals don't suffer but it also often leads to neglect of funding for research and treatment.

Our mission is to enable vital research into the causes of aplastic anaemia and other rare bone marrow failures that ultimately leads to the eradication of the diseases, and to support everyone affected by them, so they can lead healthy and fulfilling lives.

The AAT is now in the process of establishing a more formal research function, in compliance with the standards of the Association of Medical Research Charities (AMRC), to which we will be applying for membership in due course. Our currently allocated research spend is the starting point for our future research programme.

What is Aplastic Anaemia?

Aplastic anaemia (AA) is a rare and serious bone marrow failure disorder that can be fatal. Most cases are acquired but it is increasingly recognised that inherited types of AA are more common than previously thought and can present in adults, not just in children. AA may be mistaken for other bone marrow failure disorders.

In most cases, it is an auto-immune disorder, where the immune system attacks the stem cells. These cells are the 'queen bee' cells within the bone marrow making all the different type of blood cells. This results in a deficiency of the blood making cells and the consequent downstream effects of low blood counts, in all cell types.

The three main blood cells are the red blood cells, white blood cells and platelets. In aplastic anaemia, these blood cells are reduced and the stems cells in the bone marrow - replaced by fat cells. AA can be very severe, severe or non-severe.

What are the symptoms?

Deficiency in red cells causes anaemia and people affected may experience fatigue, shortness of breath, headaches and occasionally angina chest pain. A low number of white blood cells increases the susceptibility to infections, such as sinus/throat, skin and chest infections. Low platelets cause a tendency to bleed, leading to nose bleeds, unexplained bruising, blood blisters in the mouth but also serious bleeding episodes such as into the brain cavity or from the gut which can be fatal.

Who is affected?

AA can affect anyone - of any gender, of any age, but it peaks in the young, including teens and into early adulthood, and the elderly (around 60 years).

We do not definitively know the prevalence of AA in the UK, although it is estimated that between 1-2 adults will be diagnosed in every 1 million people, or over 100 in

England alone, annually. There is no formal reporting of treatments and their outcomes (other than stem cell transplants), and no routine referral system for specialist opinion.

What is the treatment?

Treatment for AA is complex, often prolonged and involves high cost medications not easily available. These include immune suppressing medications, stem cell transplantation and the newer generation drugs like 'eltrombopag.' Immuno-suppressive treatment has been the cornerstone of treatments in AA, for patients ineligible for a stem cell transplant, to stall and prevent the immune attack on the stem cells.

Missing a diagnosis of inherited AA can result in the wrong treatment that can be fatal or result in life threatening side effects and missing other possible family members who have inherited the same condition.

Treatment for inherited AA is different from acquired AA. The diagnosis of inherited AA requires special tests, including gene testing, but gene testing is not routinely available for all the currently known inherited types of AA, and research needs to continue to identify new faulty genes that may cause AA.

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3. What research will we fund and how?

Clinical research is vital for increasing our knowledge of aplastic anaemia and other rare bone marrow failures. One of the AAT's key objectives is to fund high quality research projects that have the potential to lead to improved treatments and ultimately cures.

Our research scope

Our research focus will be on rare bone marrow failure disorders, both inherited and acquired, in adult and child populations. Whilst the primary focus will be on Aplastic Anaemia, we will consider research proposals into other allied rare bone marrow failures, including Paroxysmal Nocturnal Haemoglobinuria (PNH), Fanconi Anaemia, Dyskeratosis Congenita and others, and how all these conditions may later progress to myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML).

Ultimately, our research scope will be informed by experts, and our patient and supporter community. The AAT has an active and vibrant Patient Support Group, thriving for a number of years and actively involved in our work.

Our research priorities

We will consider funding research which aims to:

1. Improve baseline understanding of rare bone marrow failures in child and adult populations.

2. Improve the understanding of the diseases by molecular/ genetic research into the damaged cells and their environment – the pathogenesis of rare bone marrow failures
3. Identify risk factors in AA patients that predispose to later MDS/AML
4. Improve treatments, identifying alternative cures, enabling experimental therapies and ultimately eradicating the diseases, including the personalisation of discovery platforms and treatments for rare BMF syndromes and AA.

In this initial research funding round, we will support both short- and medium-term projects nationally, including research fellowships – as a springboard for future work. Generally, we will consider projects from 1 to 3 years in duration.

Applications will be considered for high quality scientific and translational research projects with explicit potential to lead to improved treatments and cures for AA and allied bone marrow failures from applicants in the UK (and worldwide).

We will consider projects that act as a catalyst for opening further studies and where there is a clear gap in funding (i.e. there are no other available funding sources).

Being a modest funder of research, albeit with ambitions to grow our research programme, we will need to prioritise our funds and base our funding decisions on the scientific quality of proposed projects.

We will consider collaborative proposals where a partner institution is willing to contribute funds, with the AAT matching the funds of the other organisation to the amount agreed by the trustees.

As this is our first research strategy, we will learn from the outcomes of the first round of funding and consult with our patient and research community experts to refine our research priorities in the future.

Our research principles

In funding research, we will adhere to the principles of accountability, balance, independence, rotation and impartiality, as recommended by the Association of Medical Research Charities (AMRC).

How will we fund research?

We will have 1 funding round per year. The process and timeline will be advertised on our website and within the research community.

The level of research funded will be determined by the funds available and agreed by the Board of Trustees.

We will retain some flexibility in funding to enable us to fund joined research with others during the year if an opportunity presents itself.

How will we select research projects?

We will aim to complete the research project assessment and grand award process within 6 months.

- **At stage 1**, all applications for research received will be subject to an initial screening internally to check the research is within the AAT's remit and meets the criteria of eligibility, strategic fit and proposal completeness.
- Those successfully screened as eligible for review will then progress to **stage 2** and be sent for independent peer review to the members of our Research Advisory Panel (RAP). The RAP is AAT's scientific peer review committee, made up of independent experts with a wide variety of expertise who assess applications, produce a shortlist and make recommendations for funding to the Board of Trustees. The scientific experts will produce a short-list of promising applications and will produce detailed written feedback on those that are likely to progress to stage 3.
- Post-doctoral fellowships will not require an external peer review – in-house expertise will be relied upon.
- Our Research Advisory Panel (RAP) will then meet as part of the final assessment process at **stage 3.** RAP will evaluate proposals on the basis of three key criteria: (1) proposed research project quality, (2) impact on patients (tangible outcomes that lead to improved treatments and ultimately, cure) and (3) value to the haematology community.
- **Stage 4** will entail AAT's Board of Trustees making the final decision, based on the RAP's advice and the funds available.

How will we evaluate research effectiveness?

The impact of the research we fund will be measured in terms of achievement against original research goals, publication in highly-rated journal(s) of key research findings and review by peers at the end of a grant funding period. We will also collect the outputs of our research projects via Research Fish, an online facility that enables research funders to track the impacts of their investments, and researchers to easily log the outcomes of their work. Evaluating our research will help us continually improve as a charity.

Where possible, we will undertake visits to the research site. This will be proportionate to the size/ importance of the project.

4. **Who and how we will collaborate with**?

The AAT strongly recognises the importance of collaboration in planning and undertaking research, in rare bone marrow failures. The rarity of these diseases means that clinical trials are often international. We are already involved in many international collaborations and working groups, for example, the European Bone Marrow Transplant Group, with a joined clinical trial underway. We are also closely involved with the National Institute of Health in the US, University of Sao Paulo, Brazil and National Institute Bone Marrow Transplant Centre, Rawalpindi, Pakistan, King Faizal Hospital Cancer Research Centre, Riyadh, Saudi Arabia, University of Pavia,

Italy. Our existing relationships put us in a strong position to collaborate further with centres globally.

Applications will be welcomed from collaborative research proposals both with the UK and beyond. In these instances, we will consider matching the funds put forward by a partner institution, to the level agreed by the Board of Trustees.

5. How will we share research findings?

The AAT will aim to actively disseminate research findings to both professional and lay audiences. Our unique position as both a funder of research and provider of emotional and practical support to our patient and supporter community, puts us in a strong position to facilitate information sharing and dissemination among the clinical communities to which our work is of relevance, as well as our network of patients. We will share research findings via:

- Our website aimed at or our primary audiences – patients and their supporters and clinicians, with an emphasis on information accessibility
- AAT's E-newsletter
- Presentations in seminars and meetings
- In future, training events for professionals
- International platforms.

6. How will we review the strategy?

This being the first AAT's Research Strategy, it will be reviewed a year after its launch, to identify and incorporate any learning.

In the future, we will aim to review the strategy every three years, however, any relevant significant learning will be incorporated as we progress.