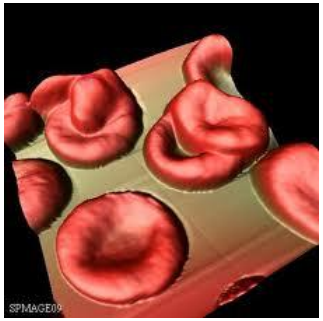
Challenges in Research



Dr Charlotte Bradbury
Consultant Haematologist, UHBristol
Senior Lecturer, CMM, University of Bristol

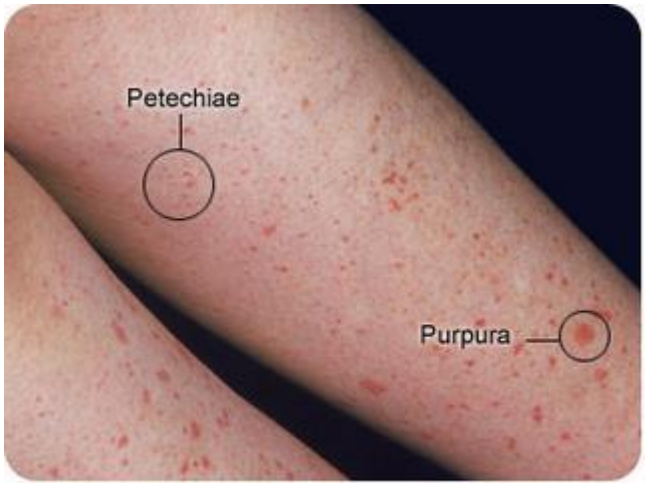
My steep learning curve

- As a new independent investigator: Where to start?
- Working at the clinical and basic science interface
- Challenges in research on rare conditions
  - Immune thrombocytopenia
  - Blood clotting problems in Leukaemia
- Navigating the research processes

What is Immune Thrombocytopenia (ITP)?

- 3/100,000 persons/year
- **Autoimmune**
  -> increased consumption & reduced production of platelets

  Low platelet count
- Abnormal bruising and bleeding, fatigue
- Diagnosis of exclusion (not always easy!)
- First-line treatment: high dose corticosteroids



http://www.caseyscause.org/images/321_purpura

First line high dose corticosteroids for ITP

Side effects

- Mood swings, difficulty sleeping, weight gain, hypertension, diabetes, gastric irritation, skin thinning, osteoporosis
- 98% of people experience >1
- 38% stop or reduce dose

Heterogeneous response

- 30% refractory
- 70–90% relapse
- Only 20% stay well long term with this approach

Unsatisfactory but unchallenged for decades

- ❑ Lack of new approaches due to a chronic lack of research
- ❑ Only research done has been funded by pharmaceutical companies
- ❑ Rare disease, non cancerous
- ❑ Mortality rare so not priority for research
- ❑ Underestimates the impact of ITP

Impact of uncontrolled ITP

For patients

Physical

- Bleeding, bruising
- Fatigue
- Treatment side effects

Psychological

- Fear of bleeding/bruising
- Appearance of bruising
- Unpredictable clinical course
- Treatment side effects
- Effect of fatigue
- Socioeconomic factors

Socioeconomic

- Time off work
- Hospital appointments
- Financial cost
- Restricted activities due to bleeding risk

Impaired Quality of Life

For health care providers

Resource use

Facilities
Staff time
Laboratory/pharmacy etc

Financial cost

Drug cost
Resource cost

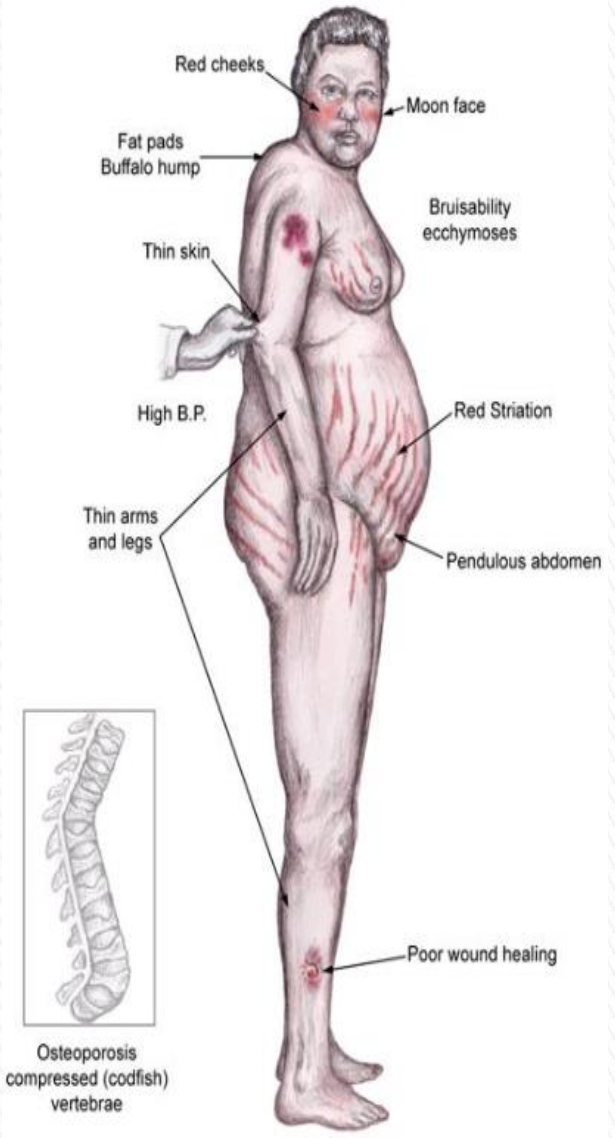
ITP: patient oriented research priorities

Bristol ITP patient group reported priorities:

- Avoid the trial and error approach to treatment
- Less corticosteroid

What are the unmet research needs?

1. Develop blood tests to help diagnose ITP
2. Develop blood tests to improve prediction of treatment response:
   - Right treatment sooner (early disease control)
   - Less side effects
   - Widely applicable to other autoimmune conditions
3. Develop blood tests to predict other clinical outcomes (bleeding, chronicity, relapse)
4. Improve first line treatment pathways



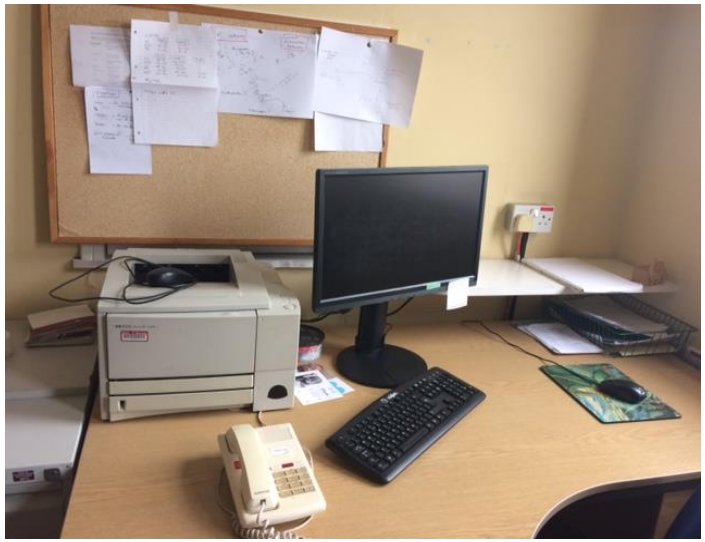
My research and clinical background

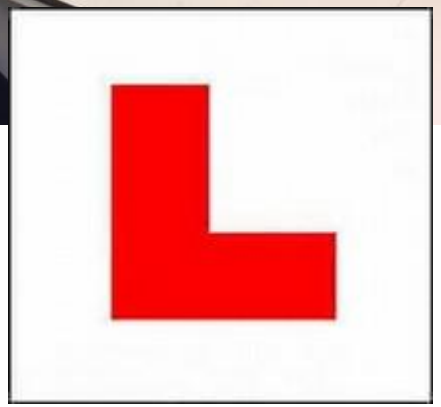
- Medicine degree (BM BCh Oxon)
- Intercalated science degree Physiological Sciences
- SHO rotation (medicine) FRCP
- Basic science PhD (Leukaemia Research training fellow)
  - Chromatin and gene expression in Acute Myeloid Leukaemia
- Haematology specialist training FRCPath
- Final SpR year appointed as a haemostasis fellow UHBirmingham
- Ongoing involvement in clinical and laboratory research as a haematology specialist trainee

Consultant Senior Lecturer (Haematology) advertised

- Wasn't planning on relocating to Bristol
- Blood clotting, research, teaching – sounds a perfect combination!
- Invited for a visit and really liked the department and city
- Applied and appointed April 2014

Where to start?





Realisation:

- No previous grant application experience
- No previous ethics applications
- Never led research projects
- No post doctoral laboratory experience
- Empty laboratory with no “critical mass”
- Only experience of clinical trials was consenting patients as a SpR

I have no idea what I am doing!!!

Getting started

Funding opportunities for new researchers in Bristol

David Telling
Charitable trust

Elizabeth Blackwell Institute

Started with funding and ethics applications for 2 Observational studies:

Low platelet blood study (ITP): Funding EBI and Above and Beyond.
Recruited 68 patients in 12m. Data accepted for presentation ASH 2017
Pilot data formed the basis of successful grant applications to BMA and ITP support association

GlobALL study (thrombosis in acute leukaemia): Funding Above and Beyond and David Telling Charitable trust
Recruited 35 patients in 12m. Data presented at BSH and ISH and published 2017

Getting connected: Nationally and locally with clinicians, researchers, patient groups.

Scaling up to multicentre CTIMP

•Mycophenolate MMF is a commonly used second line treatment for ITP.

•MMF is effective in 50-80% and well tolerated but acts slowly, taking up to 2 months to take effect.

•MMF is generic and cheaper than most other second line treatments (e.g. TPO mimetics and Rituximab)

•Why not try commencing MMF at the beginning with steroid with an aim to prevent the almost inevitable relapse and compare with steroid alone?

•Discussed idea locally and nationally and it was fully supported by clinicians and patient groups

•Spoke to RDS statistician (Rosemary) who was supportive and very helpful at talking through next steps.

Everyone thought it was a great idea……

BUT….Many reasons to give up along the way!

- Limited funding options: ITP is rare, non cancerous and rarely impacts survival, no pharma interest in MMF and CI had no track record (me!).
- NIHR RFPB application was considered the best option
- But budget and timelines are tight
- Multicentre trial is necessity to get patient numbers
- Difficulty funding multicentre CTIMP within RfPB
- Difficulty achieving sample size needed within RfPB timelines
- Initial plan for Placebo controlled RCT wasn't an option (cost and patient feedback)
- Difficulty getting a CTU on board with the research proposal (3 would not do within a RFPB budget)
- Finally, Cardiff CTU agreed to run the study and have been brilliant!

Navigating the processes

FLIGHT trial

- Application to NIHR was successful for funding
- Protocol, patient information, consent forms
- Applications to REC, MHRA, HRA, ISRCTN
- Application for sponsorship
- Contracts
- Case report forms
- Capacity and capability
- Plentiful risk assessments!
- SUMP (study set up and management plan)
- Database set up and testing
- Pharmacy review
- Etc etc etc

To make it more complicated – I insisted on adding a translational basic science laboratory study based on our pilot data!

Current status: >40 sites in UK in the process of being set up

Translational sub study ready to go

Key to survival as a new researcher

- Talk through research ideas with the right people
- Get connected locally and nationally including with patient groups
- Collaborate with other research groups with relevant expertise
- Get a good team around you (including people with experience)
- Know your strengths and weaknesses

Other essentials

- Stamina for paperwork
- Teflon coating
- Tea and cake with Elinor and Rosemary

A massive thanks particularly to Rosemary Greenwood, Elinor Griffiths, Julie Pell (Cardiff CTU), Katharine Wale, Richard Lee, Maddie Stimpson and the rest of the team