Immunology
A Medical Speciality in The UK

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Objective!

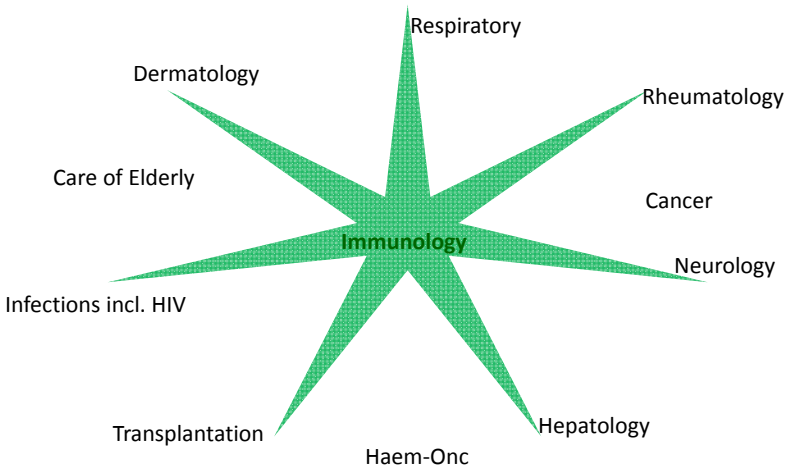
- Understand the practice of clinical immunology in the UK as a medical or clinical scientific speciality
- Have a feel for what it is practically like as an immunologist
- Ask questions and discuss immunology careers

Topics

- Introduction
- What to do to be an Immunologist?
- What does an Immunologist do?
- Conclusion
- Discussion

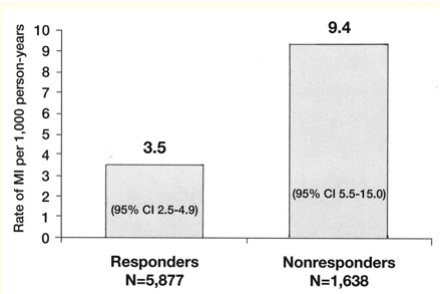
INTRODUCTION

Immunological Mechanisms: vast spectrum of disease



Immunology is a cross-cutting specialty

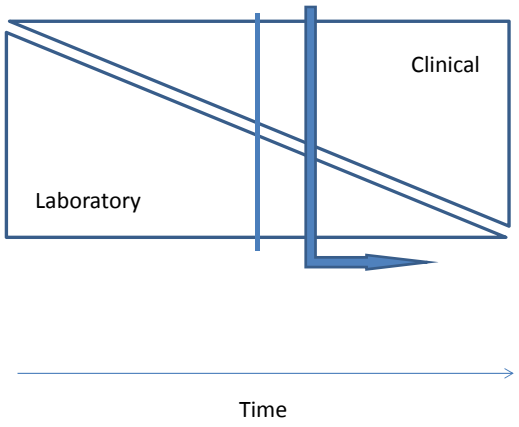
Less Myocardial Infarction in responders to anti-TNF



Incidence rates of first myocardial infarction (MI) in responders and non-responders to anti-tumour necrosis factor treatment.

Dixon WG, *et al*. Arthritis Rheum 2007;56:2905-12

Journey of Immunology as a UK Medical Specialty over 30-40 years



The Royal College of Pathologists

Pathology: the science behind the cure

Immunology

- Basic scientific knowledge has grown fast in the last three decades
- Medical applications of basic science are emerging in diagnostic and therapeutic areas of medicine
- Field is dynamic and changing all the time through new discoveries of cells, processes and molecules

HOW TO ENTER IMMUNOLOGY TRAINING IN THE UK?

For Medics

- MB BS
- ± BSc (optional)
- FY1 & FY2
- CMT1 & CMT2
- MRCP or equivalent (mandatory)
- Competitive National Recruitment for ST3

For Scientists

(To become a Trainee Laboratory-Based Clinical Scientist in Immunology)

- Level 1 (Competitive National Interview):
  - BSc
- Level 2 (Competitive National Interview):
  - BSc
  - MSc
  - ± PhD (optional for entry, but has to be done during training)

WHAT HAPPENS WHEN YOU ARE IN!

SPECIALTY TRAINING CURRICULUM

FOR

IMMUNOLOGY

2015

(Approved 4 November 2015)

Joint Royal Colleges of Physicians Training Board

5 St Andrews Place
Regent's Park
London NW1 4LB

Telephone: (020) 3075 1621
Email: curriculum@jrcptb.org.uk
Website: www.jrcptb.org.uk

2015 Immunology curriculum Example of Competencies

- Common competencies
- 1.1 History Taking
- 1.2 Clinical Examination
- 1.3 Therapeutics and Safe Prescribing
- 1.4 Time Management and Decision Making
- 1.5 Decision Making and Clinical Reasoning
- 1.6 The Patient as Central Focus of Care
- 1.7 Prioritisation of Patient Safety in Clinical Practice
- 1.8 Team Working and Patient Safety
- 1.9 Principles of Quality and Safety Improvement
- 1.10 Infection Control
- 1.11 Managing Long-Term Conditions and Promoting Patient Self-Care
- 1.12 Relationships with Patients and Communication within a Consultation
- 1.13 Breaking Bad News
- 1.14 Complaints and Medical Error
- 1.15 Communication with colleagues and cooperation
- 1.16 Health Promotion and Public Health
- 1.17 Environmental Protection and Emergency Planning
- 1.18 Principles of Medical Ethics and Confidentiality
- 1.19 Obtaining of Consent

Workplace - Based Assessments

- Multi-Source Feedback (MSF)
- Multiple Consultant Report(MCR)
- mini-Clinical Evaluation Exercise (mini-CEX)
- Direct Observation of Procedural Skills (DOPS)
- Case-Based Discussion (CbD)
- Patient Survey (PS)
- Audit Assessment (AA)
- Teaching Observation (TO)
- Quality Improvement Project Assessment Tool (QIPAT)

Usual Start!

- First few months - training in diagnostic Immunology Laboratory
  - Immunochemistry
  - Immunofluorescence
  - Flow cytometry
- Regularly authorise laboratory results
- Specialist clinics
  - primary immune deficiency
  - immunoglobulin therapy infusion
  - Allergy: including drug allergy, immunotherapy and drug/food challenges
  - systemic autoimmune disease and vasculitis

A Bit More Advanced!

- Clinical meetings, including MDMs & Grand Rounds
  - Present clinical cases & audits
  - Discuss challenging clinical scenarios
- Specialist attachments
  - 3 months Paediatric Immunology @ GOS
  - Specialist Vasculitis, haem-onc clinics
  - Other centres to broaden experience

Additional Activities

- MSc – Immunology
  - Usually done part time during training
- PhD – Immunology
  - Usually done as Out of Programme Experience (OOPE)
  - 3 – 4 years
- Other OOPE
  - Visiting specialist centres, developing special interest, or anything if you can persuade the Deanery

Exit Examination

FELLOWSHIP OF THE ROYAL COLLEGE OF PATHOLOGISTS (FRCPATH)

Format of the FRCPath Immunology Part 1 Examination

- The Part 1 examination comprises a written examination:
- There are two three-hour written papers, comprising short-note style questions and structured essay-style questions.
- Paper 1 will examine the knowledge of scientific principles underpinning the practice of clinical and diagnostic immunology. All candidates will be required to answer this paper.
- Paper 2 will test the knowledge of the clinical aspects of immunology and will comprise of two alternative versions. The first version, which is for medically qualified candidates, will include questions that address both the clinical and laboratory assessment, and the treatment of patients with disorders of the immune system. The second version, for non-medical candidates, will replace those questions requiring in knowledge of clinical assessment and treatment with alternative questions concerning the effective delivery of diagnostic immunology services. may include clinical features of disease and principles of treatment. It is axiomatic that the two versions will share some questions.

FRCPath Immunology Practical Examination

- Standard of the practical examination
- The examination will test the ability of candidates to function as an independent practitioner in the field of diagnostic laboratory Immunology.
- Marking of the practical examination
- For each station a panel of examiners will determine the pass standard using a modified-Angoff method. Candidates will have to achieve a pass in all stations (or the majority of stations with limited compensation) to secure an overall pass in the examination.

FRCPath Immunology Oral Examination

- The **oral examination** will have an objective structured format and will not duplicate topics that are *better* covered by the practical examination. The oral examination will last for 60 minutes and will be conducted by two pairs of examiners, 30 minutes being spent with each pair of examiners.
- **Communications skills** essential for immunologists and it is important that both medical and non-medical trainees develop their clinical liaison skills to enable them to offer appropriate clinical advice to their colleagues, and to think through the consequences of advice for patient management. Medical candidates will be asked questions on the clinical management of patients with diseases of the immune system.

Marking of the oral examination

- Section one:
  - Two Diagnostic problems (50% of marks). One will be Immunology, and one will be an allegy clinical scenario.
  - Communication with patients and relatives, and ethical issues to be included
  - Treatment and complications to be included
- Section two:
  - Laboratory Quality assurance (25% of marks)
  - Scientific, translational and technological advances (25% of marks)
  - Candidates will have to achieve a pass in both sections to secure an overall pass in the oral examination.

Immunology Written Project

- The written module, of the Part 2 examination will be one of the following options:
- (a) PhD/MD thesis, normally completed during the training period
- (b) a series of refereed, published papers (or in press)
- (c) a casebook comprising 4 clinical cases, 1 audit, 1 lab practice, 1 management or communication and 1 optional of any

WHAT HAPPENS WHEN YOU BECOME AN IMMUNOLOGIST?

What is Clinical Immunology?

The clinical practice of immunology, as defined by the **World Health Organization**, encompasses clinical and laboratory activities dealing with the study, diagnosis, and management of patients with diseases resulting from disordered immunological mechanisms, and conditions in which immunological manipulations form an important part of treatment

In Some Cases!

- A minority of immunologists (< 10%) also provide laboratory support for transplantation by histocompatibility leukocyte antigen (HLA) typing
- Support for the diagnosis and management of conditions such as:
- autoimmune diseases such as Type-1 diabetes or rheumatoid arthritis or inflammatory bowel disease
- human immunodeficiency virus (HIV)
- other severe/systemic infections
- multiple sclerosis
- tuberculosis

History

- 41 year old right handed male
- Lorry driver, works with sewage
- Presented with 3 week history of difficulty walking, left sided weakness and sensory disturbance
- Found to be anaemic by GP and treated with iron

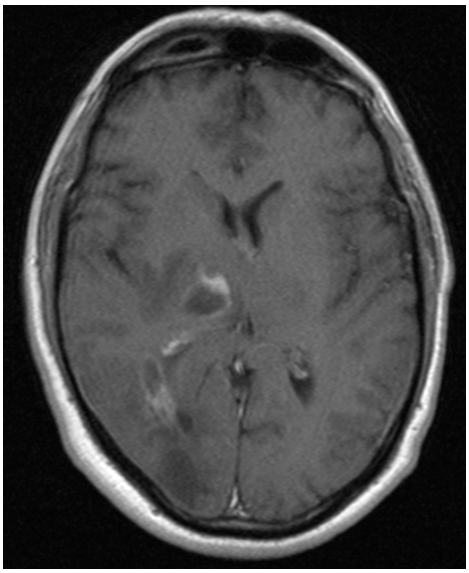
Past History

- Recurrent boils between age 18-20
- Morning cough
- Otherwise previously generally fit and well

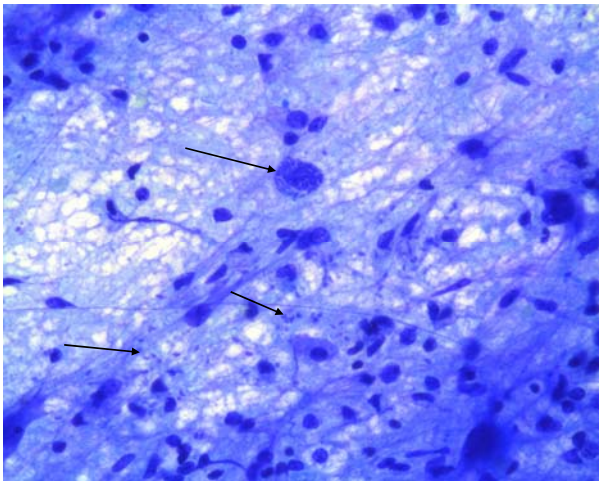
- Medication
  - Fe sulphate 200 mg tds
  - Omeprazole

MRI

Right thalamic lesion showing patchy, mainly peripheral, enhancement
Considerable peri-lesional oedema particularly affecting right occipital lobe
Strands of abnormal tissue passing more posteriorly
May represent primary tumour, possibly glioblastoma, particularly with short history



Cyst and free organisms



Diagnosis

Cerebral toxoplasmosis

Further Investigations

- Lymphocyte subsets
  - CD4 623, CD8 433, B cells 75, NK cells 36
- Immunoglobulins
  - IgG 2.75 (7.00 – 18.60)
  - IgA 0.57 (0.78 – 4.80)
  - IgM 2.58 (0.49 – 2.00)
- No paraprotein detected

Hyper IgM syndrome

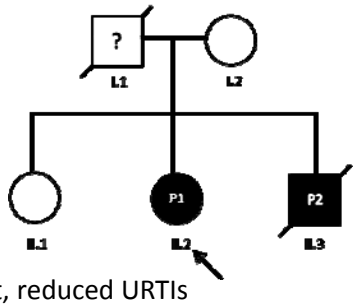
- Combination of opportunistic infection and immunoglobulin pattern suggestive of this
- Group of immunodeficiency syndromes due to a defect in immunoglobulin class switch recombination from IgM (made in a primary immune response) to IgG/A/E (made in a secondary immune response)
- Characterised by low levels of IgG/IgA but high or normal levels of IgM

Examples of Biologics in Immunology!

- Therapeutic monoclonal antibodies (Kohler & Milstein)
  - Rituximab, infliximab, omalizumab, … etc.
- Artificial chimaeric recombinant fusion proteins
  - CTLA4-Ig (abatacept)
  - TNFR-Ig (etanercept)

Summary of Family History - I

- **Greek Cypriot family of non-consanguineous parents with 3 children**
- **Proband**, female
- 14 months: severe chickenpox
- Frequent URTIs
- Frequent diarrhoeas, no specific infection
- 3 years: shingles
- 4 years: alopecia totalis
- 9 years: diagnosed CVID, IVIG replacement, reduced URTIs
- 12 years: high resolution CT chest, progression of bronchiectasis
- 15 years: idiopathic thrombocytopenic purpura (ITP, 4 episodes) Responds to rituximab, but not corticosteroids, high dose IVIG or anti-D
- 22 years: postural hypotension, cortisol & ACTH deficiency, hydrocortisone replacement

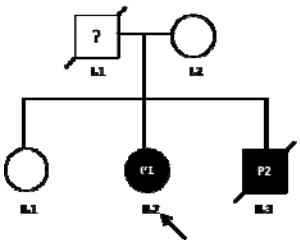


(Liu et al., J Clin Immunol (2014) 34:686–69

Subjects	I.2[a]	II.1	II.2	II.3
Immunoglobulins				
IgG (6.34 – 18.11 g/L)[b]	NA	6.71	3.01	4.70
IgA (0.87 – 4.12 g/L)	NA	0.84	< 0.07	< 0.07
IgM (0.53 – 2.23 g/L)	NA	0.59	0.14	0.14
IgE (< 100 IU/L)	NA	126	< 20	< 20
Vaccination responses				
Haemophilus influenza type b (> 0.14 mg/L)	NA	> 9	3.0	2
Tetanus (> 0.14 IU/ml)	NA	> 7	2.9	2.3
Pneumococcal (serotypes with ≥ 1.5 mcg/ml IgG)	NA	8	NA	2
Lymphocyte subsets				
Lymphocytes (1300 – 4000 × 10^6/L)	NA	2481	2369	2142
CD3+ (723 – 2737 × 10^6/L)	NA	1940	2276	1976
CD4+ (404 – 1612 × 10^6/L)	NA	1284	1256	1035
CD8+ (220 – 1129 × 10^6/L)	NA	578	979	908
CD16+ CD56+ NK cells (84 – 724 × 10^6/L)	NA	176	51	99
CD19+ (80 – 616 × 10^6/L)	NA	365	42	67
CD27−IgD+ naive B cells (% of CD19+)	58.0	65.7	81.4	NA
CD27+IgD+ marginal zone/non-switched memory B cells (% of CD19+)	27.2	25.3	17.5	NA
CD27+IgD− switched memory B cells (% of CD19+)	12.9	7.9	0.5	NA
CD4+CXCR5+ Tfh cells (% of CD4+)	52.6	40.6	4.4	NA
CD4+CXCR5+ICOS+PD-1+ (% of CD4+)	31.5	23	1.5	NA
Adrenal hormonal investigation				
Cortisol (morning, 130 – 580 nmol/L)	NA	227	< 30	NA
ACTH (morning, 5 – 46 ng/L)	NA	NA	< 5	NA

(Liu et al., J Clin Immunol (2014) 34:686–690)

Laboratory Findings

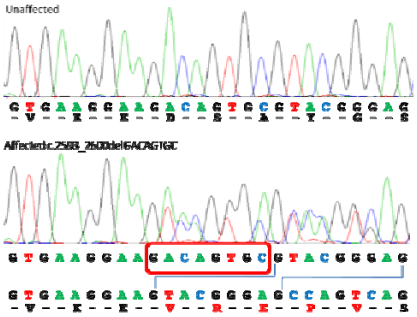


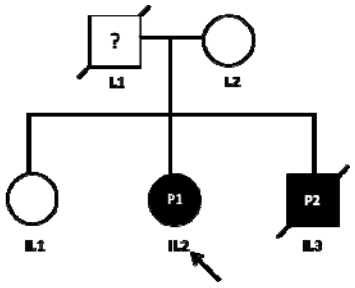
[a] subject identifiers as provided in the family tree.
[b] reference intervals according to KingsPath medical laboratories.

Abbreviations: NA, not available; NK, natural killer; IgD, immunoglobulin D; CXCR5, chemokine (C-X-C motif) receptor 5; Tfh, T follicular helper; ICOS, inducible T-cell costimulator; PD-1, programmed cell death 1; ACTH, adrenocorticotrophic hormone.

Whole Exome Sequencing identified a heterozygous mutation in NFKB2

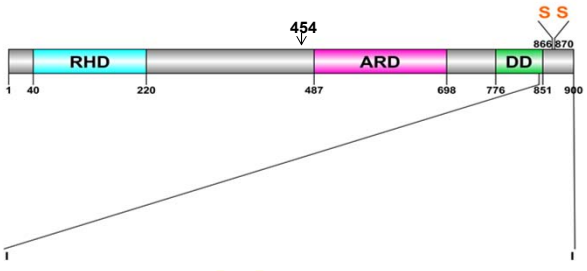
- Primary candidate was a deleterious mutation in the C-terminal part of ***NFKB2*** gene (read depth 74)
- Dye-termination sequencing confirmed that the *NFKB2* mutation **c.2593_2600delGACAGTGC** was present in both affected siblings
- Heterozygous 8 bp deletion predicted to cause a frameshift and premature stop codon (p.Asp865Valfs*17) resulting in a truncated protein (881 aa), 19 amino acids shorter than wild type (900 aa), p100Δ19





(Liu et al., J Clin Immunol (2014) 34:686–69

Predicted NFκB protein change

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Human           845  RLLRGPETRDKLPSTAEVKEDSAYGSQSVE-QEAEKLGPPPEPPGGLCHGHPQPQVH  900
Human p100Δ19   845  RLLRGPETRDKLPSTAEVKEVREPVSGAGG-REAG---PTP----------------  881
Mouse           845  RLLKGPETRDKLPST-EVKEDSAYGSQSVE-QEAEKLCPPPEPPGGLCHGHPQPQVH  899
Mouse Lym1      845  RLLKGPETRDKLPST-EVKEDSA-------------------------------  866
Chicken         851  RMLRKPEPLEKLQST-EVKEDSAYGSESVEEEQAARLKPRPVPEGELPHSQQQQQVH  906
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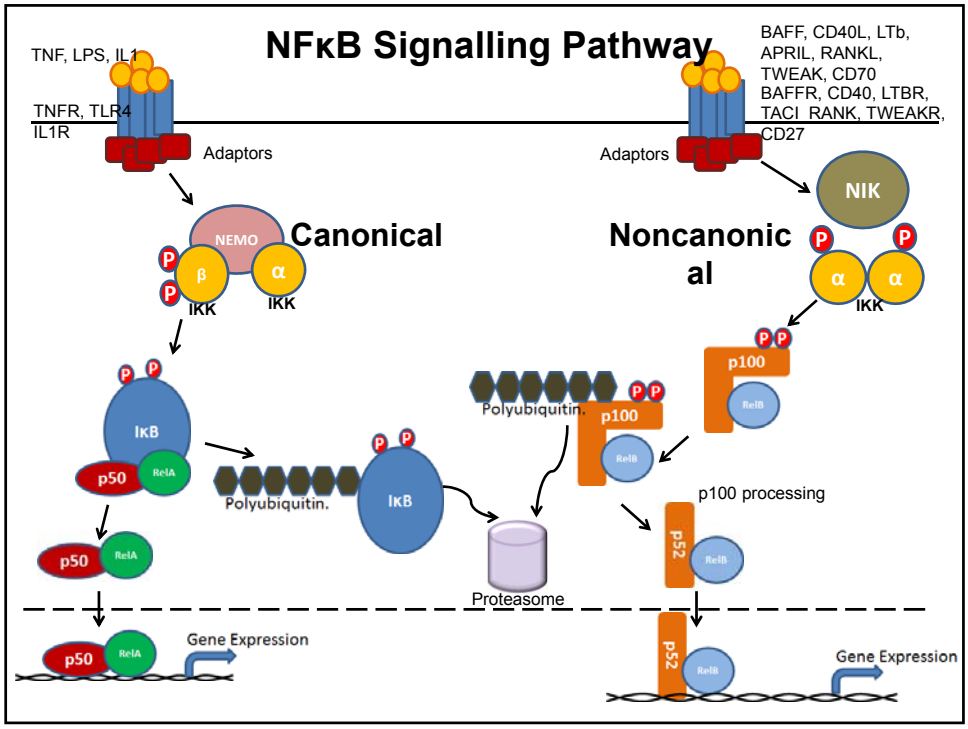
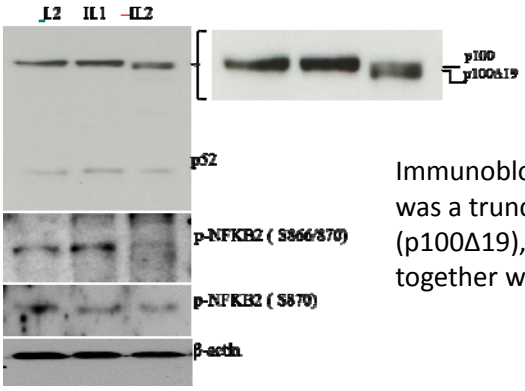
(Liu et al., J Clin Immunol (2014) 34:686–69



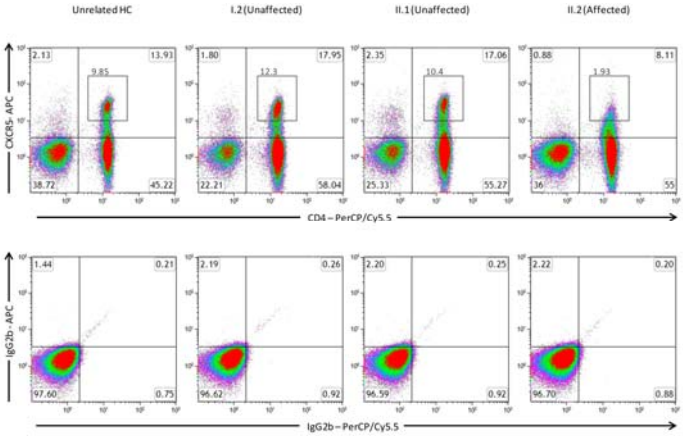
NF-κB2 Mutation



Immunoblotting confirmed that there was a truncated form of p100 (p100Δ19), only present in patient P1, together with wild type p100

(Liu et al., J Clin Immunol (2014) 34:686–6

Reduced numbers of circulating T follicular helper (Tfh) cells in the peripheral blood of a patient with a mutation in *NFKB2* and CVID (II.2 Affected)



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Other Fates for Immunologists!

- Industry (Pharmaceutical Companies)
- Full-time in Private Practice

Conclusion

- Immunology is both a clinical and laboratory-based medical speciality.
- Training is a 5 year programme, with an optional out of programme period.
- This commences with entry at ST3 level after Core Medical Training is completed and having achieved MRCP or equivalent.
- The practice includes immunodeficiency, allergy, systemic autoimmune disease and diagnostic laboratory immunology.

Sources of Further Information

- Royal College of Pathologists
  - https://www.rcpath.org/trainees/examinations/examinations-by-specialty/immunology.html
- Joint Royal College of Physicians Training Board (JRCPTB)
  - https://www.jrcptb.org.uk/specialties/immunology
- Royal College of Physicians
  - https://www.rcplondon.ac.uk/education-practice/advice/specialty-spotlight-clinical-immunology