

**Interleukin 7:
A Proposed Role in Primary
Immune Thrombocytopenia
Thesis**

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Dedication

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List of Abbreviations

| Abb | Full Term |
|--------------|--|
| AA | Aplastic Anemia |
| ADAM | A Disintegrin And Metalloprotease with |
| TS | Thrombospondin |
| ADP | Adenosine Diphosphate |
| ANA | Antinuclear antibodies |
| aPTT | Activated partial thromboplastin time |
| ATG | Antithymocyte globulin |
| ATIII | Antithrombin III |
| ATP | Adenosine triphosphate |
| BFU- MK | Burst-forming unit-megakaryocyte |
| BFU- MK | MK burst-forming unit |
| BUN | Blood urea nitrogen |
| CAMT | Congenital Amegakaryocytic Thrombocytopenia |
| CBC | Complete blood count |
| CFU- GEMM | Colony-forming unit |
| CFU- MK | Colony-forming unit-megakaryocyte |
| CMP | Common myeloid progenitor |
| CV | Coefficients of variation |
| CXCR4 | Chemokine type 4 receptors |
| DIC | Disseminated Intravascular Coagulopathy |

| | |
|-------|---|
| DITP | Drug-induced thrombocytopenia |
| DMS | Demarcation membrane system |
| EDTA | Ethylene diamine tetra acetic acid |
| ELISA | Enzyme-linked immunosorbent assay |
| FDP | Fibrin degradation products |
| GDP | Guanosine diphosphate |
| GP | Glycoprotein |
| GTP | Guanosine triphosphate |
| HCV | Hepatitis C virus |
| HIPA | Heparin-induced platelet aggregation test |
| HIT | Heparin -induced thrombocytopenia |
| HIV | Human immune deficiency virus |
| HLA | Human leukocyte antigens |
| HPA | Human Platelet Antigen-1a |
| HSC | hematopoietic stem cell |
| HUS | Haemolytic uraemic syndrome |
| HUS | Hemolytic uremic syndrome |
| IC | Intracranial |
| Ig | Immunoglobulin |
| IL7 | interleukin 7 |
| IL8 | interleukin 8 |
| ITP | Idiopathic Thrombocytopenic Purpura |
| IWG | International Working Group |
| KMS | Kasabach-Merritt Syndrome |
| LDH | Lactate Dehydrogenase |
| MHC | Major histocompatibility complex |
| MPV | Mean platelet volume |
| NAIT | Neonatal alloimmune thrombocytopenia |
| NAP-2 | Neutrophil activating peptide 2 |
| No | Nitric oxide |

| | |
|------------------|---|
| PAF | Platelet activating factor |
| PAI-1 | Plasminogen activator inhibitor-1 |
| PCR | Polymerase chain reaction |
| PDGF | Platelet-derived growth factor |
| PF4 | Platelet factor 4 |
| PGI ₂ | Prostaglandin I ₂ |
| POP | Post transfusion purpura |
| PT | Prothrombin time |
| PTP | Post transfusion purpura |
| SCCS | Connected canalicular system |
| SLE | Systemic lupus erythematosis |
| TF | Transcription factors |
| TFPI | Tissue factor pathway inhibitor |
| TGF- β | Transforming growth factor- β |
| TMA | Thrombotic microangiopathies |
| tPA | Tissue plasminogen activator |
| TPO | thrombopoietin |
| TSH | Thyroid stimulating hormone |
| TSP1 | Thrombospondin-1 |
| uPA | Urokinase plasminogen activator |
| VEGF | Vascular endothelial growth factor |
| VWF | von Willibrand factor |
| TSLP | Thymic stromal lymphopoietin |
| RT-PCR | Reverse transcription polymerase chain reaction |
| PBMCs | Peripheral blood mononuclear cells |
| BMNCs | Bone marrow mononuclear cells |
| IFN-g | Interferon-g |
| TNF-a | Tumor necrosis factor-a |

| | |
|------|---|
| CTL | Cytotoxic T lymphocyte |
| GWAS | Genome wide association studies |
| MS | Multiple sclerosis |
| T1D | Type 1 diabetes |
| RA | Rheumatoid arthritis |
| IBD | Inflammatory Bowel Disease |
| ROC | Receiver operating characteristic curve |
| Sn | Sensitivity |
| Sp | Specificity |
| PPV | Positive predictive value |
| NPV | Negative predictive value |
| TH1 | T helper 1 |
| TH2 | T helper 2 |

Introduction

Primary ITP is an autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count $<100 \times 10^9/L$) in the absence of other causes or disorders that may be associated with thrombocytopenia (*Rodeghiero et al., 2009*).

The diagnosis of primary ITP remains one of exclusion; no robust clinical or laboratory parameters are currently available to establish its diagnosis with accuracy (*Cooper et al., 2006*).

The dominant clinical manifestation is bleeding, which correlates generally with severity of the thrombocytopenia. Most cases are considered primary (Thereafter designated ITP), whereas others are attributed to coexisting conditions (secondary immune thrombocytopenia) (*Stasi and Evangelista et al., 2008*).

The disease and its most widely accepted abbreviation, ITP, has variably been defined as “immune thrombocytopenic purpura”, “idiopathic thrombocytopenic purpura”, and most recently “immune thrombocytopenia” (*Ruggeri et al., 2008*).

An International Working Group (IWG) consensus panel of both adult and pediatric experts in ITP recently provided guidance on terminology, definitions, and outcome criteria for this disorder.

The IWG defines ITP as newly diagnosed (diagnosis to 3 months), persistent (3 to 12 months from diagnosis), or chronic (lasting for more than 12 months) (*Rodeghiero et al., 2009*).

Historically, ITP was believed to be caused by increased platelet destruction at a rate that exceeded production by a compensating bone marrow. New knowledge has questioned this model, providing evidence that platelet production is also decreased in many patients with ITP (*Bromberg, 2006*).

The pathology of ITP is heterogeneous and complex. Besides auto-reactive B lymphocytes secreting antiplatelet antibodies and being considered as the primary immunologic defect in ITP, abnormality of cellular immunity, such as increased Th1/Th2 ratio, T-cell-mediated platelet lysis and reduced numbers and poor functions of circulating regulatory T cells (Tregs), has also been widely demonstrated in ITP (*Hui-Yuan et al., 2014*).

Interleukin 7 (IL-7), a member of IL-2 family, is produced by bone marrow stromal and epithelial cells (*Bradley et al., 2005*). It acts through a receptor that is comprised of two chains: IL-7R alpha (CD127) and gamma chain (CD132). IL-7R is highly expressed on resting T cells except CD4+CD25+ Tregs (*Seddiki et al., 2006*).

IL-7 is critical for T-cell development, survival,