Preface

Allergy-related diseases are today recognized as reaching epidemic proportions, with up to 30% of the general population suffering from clinical symptoms ranging from urticaria, rhinitis and asthma to life-threatening anaphylactic reactions.

The main contributors to the increasing prevalence of allergy seem to be very diverse including increasing immunological predisposition (‘atopy’), changing food consumption and well as living conditions. The dramatic increase of allergic diseases is not only seen in the developed world, but increasing evidence indicates that also developing countries are considerably affected. Already over fifty percent of the world population is living in Asia, where not only food consumption, but also food allergies are very different from what is mainly published from Western countries. In the research efforts in the field of food allergy two main questions are often asked: What makes one person allergic to a particular food and not the other? Furthermore, Why are some foods and food proteins more allergenic than others? In addition it is very difficult to predict the severity of clinical reaction and the amount of allergen required to elicit these reactions.

Major food allergens from a small number of sources were identified and purified as early as the 1970s. A boost in the number of newly identified allergens was elicited by the general availability of recombinant DNA technology in the late 1980s. The ever-growing IUIS Allergen Nomenclature Database contains currently over 840 allergens from 252 sources and their isoforms and variants. Currently we know about 290 food allergens from 98 different food sources.
Recent developments into the molecular nature of allergenic proteins enabled us to classify most allergens into few protein families with limited biochemical function. Allergenic proteins can be classified into approximately 130 Pfam protein families, while the most important plant and animal food allergens can be found in 8 protein superfamilies and is discussed in detail in Chapters 1 and 2.

The correct diagnosis of a food allergy can be complex, but includes a convincing clinical history as well as the presence of elevated levels of specific IgE antibody to allergenic proteins in a given food. Therefore, detailed knowledge about the food specific allergenic proteins is central to a specific and sensitive diagnostic approach. The different allergens of peanut, egg, fish, shellfish and food contamination parasites and their diagnostic application are detailed in Chapters 3 to 7.

The food industry is one of the largest employers of workers with about 10% and therefore is the allergic sensitisation to food borne proteins at the workplace not surprising. Workers at increased risk of allergic sensitisation include farmers who grow and harvest crops; factory workers involved in food processing, storage and packing; as well as those involved in food preparation (chefs and waiters) and transport and is detailed in Chapter 8.

Research in food allergies and allergens is much more complex than investigating inhalant allergens since food proteins often undergo extensive modifications during food processing. Furthermore these allergenic proteins are embedded in a complex matrix and may undergo physicochemical changes during digestion and subsequent uptake by the gut mucosal barrier and presentation to the immune system, and have been highlighted in Chapter 9.

Furthermore, food processing results often in water-insoluble proteins, which makes the traditional serological analysis of allergenicity difficult as well as detection and quantification in the food matrix. The approaches and problems of quantifying allergen residues in processed food are detailed in Chapter 10.

To characterize allergens better but also develop better diagnostic and therapeutics, recombinant allergens are increasingly utilized.
Unlike natural allergens or allergen extracts, the production of recombinant proteins is not dependent on biological source material composed of complex mixtures of allergen isoforms. The use of recombinant allergens has revolutionized diagnosis, enabling clinicians to identify disease eliciting allergens as well as cross-reactivity pattern, thereby providing us with the tools necessary for personalized allergy medicine and therapeutics and is detailed in Chapter 11.

Food allergy is a growing problem globally carrying a huge socioeconomic burden for patients, families and the community. Although fatalities are fortunately rare, the fear of death is very real for each patient. Currently, there is no cure for any food allergy available, with management strategies focusing on complete avoidance and utilization of adrenaline as the emergency antidote for anaphylaxis. There is a very strong imperative for safe and effective specific therapeutics for food allergy and one strategy based on T-cell epitopes for peanut allergy is detailed in Chapter 12.

We hope that the joined effort by the authors will not only provide pragmatic information for current food allergy research but also serves as a foundation for significant new research that will advance our current knowledge.
## Contents

*Preface*  

1. Biomolecular and Clinical Aspects of Food Allergy  
   *Heimo Breiteneder*  
   1.1 Introduction  
   1.2 Prolamin Superfamily  
      1.2.1 Prolamins  
      1.2.2 Bifunctional Inhibitors  
      1.2.3 2S Albumins  
      1.2.4 Nonspecific Lipid Transfer Proteins (nsLTPs)  
   1.3 Cupin Superfamily  
      1.3.1 Vicilins (7S globulins)  
      1.3.2 Legumins (11S globulins)  
   1.4 EF-hand Superfamily  
      1.4.1 Parvalbumins  
   1.5 Tropomyosin-like Superfamily  
   1.6 Profilin-like Superfamily  
   1.7 Bet v 1-like Superfamily  
   1.8 The Casein and the Casein Kappa Family  
   1.9 Calycin-like Superfamily  
      1.9.1 Lipocalins  
   1.10 Conclusions  
Acknowledgement  
References  

2. Nomenclature of Food Allergens  
   *Christian Radauer*  
   2.1 Introduction  
   2.2 Allergen Nomenclature  
      2.2.1 Origin
2.2.2 Genus and Species Names 33
2.2.3 Allergen Numbers 33
2.2.4 Isoallergens and Variants 34

2.3 Submitting New Allergens to the WHO/IUIS Allergen Database
2.3.1 Allergen Source 36
2.3.2 Sequence Data 38
2.3.3 Tested Patient Population 38
2.3.4 Sensitization to the Submitted Allergen 38

2.4 Conclusions 39

References 39

3. **Nut Allergy**

_Dwan Price, Wesley Burks and Cenk Suphioglu_

3.1 Introduction 42
3.2 Why are Nut Allergens so Allergenic? 43
3.2.1 Allergen Abundance 44
3.2.2 Complex Structural Integrity 44
3.2.3 Special Allergen Attributes 44
3.3 What Therapies are Currently Addressing Nut Allergy? 45
3.4 Exploring Causes of Nut Allergy 46
3.4.1 Breaking Down Barriers 46
3.4.1.1 Increased intestinal permeability 46
3.4.1.2 Dermal barrier failure 49
3.4.2 Initial Allergen Encounters—Is the Timing of Allergen Introduction Important? 49
3.4.2.1 _In utero_ 49
3.4.2.2 Breast milk 50
3.4.2.3 Early foods 51
3.4.3 Immune System Development—Preparing the Gut for Nut Allergen Contact 52
3.4.3.1 The mucosal response to microbe colonization and gut development 52
3.4.3.2 Normal establishment of the microbiome 53
3.4.3.3 Living conditions 54
3.4.3.4 Birth type 54
3.4.3.5 Infant feeding practices 55
3.4.3.6 Antibiotics 55
3.4.3.7 Probiotics 57
3.5 Conclusions 58
References 59

4. Egg Allergy 70
Paul J. Turner and Dianne E. Campbell

4.1 Introduction 71

4.2 Egg Protein Allergens: Composition and Chemistry 71
  4.2.1 Egg White 72
  4.2.2 Egg Yolk 74

4.3 Primary Prevention of Egg Allergy 75

4.4 IgE-mediated Egg Allergy 76
  4.4.1 Prevalence and Natural History 76
  4.4.2 Diagnosis 78
  4.4.3 Treatment 80
    4.4.3.1 Immunotherapy 80
    4.4.3.2 Vaccinations and medications containing Egg 81

4.5 Non IgE-Mediated Food Allergy 82
  4.5.1 Food protein Induced Enteropathy Syndrome (FPIES) 82
  4.5.2 Eosinophilic Oesophagitis (EoE) 83
  4.5.3 Eczema 84

References 85

5. Fish Allergy 95
Annette Kuehn and Karthik Arumugam

5.1 Introduction 96
  5.1.1 Fish, a Staple Food 96
  5.1.2 Adverse Reactions to Fish: Intoxication and Allergy 97
  5.1.3 IgE-mediated Fish Allergy: Clinical Phenotypes 100
  5.1.4 Fish Allergy Diagnosis and Therapy 102

5.2 Fish Allergens 104
  5.2.1 Parvalbumins 104
  5.2.2 Fish Gelatin 107
5.2.3 Enolases and Aldolases
5.2.4 Other Fish Allergens

5.3 Translational Aspects: From Bench to Bedside
5.3.1 Allergen Contents in Food
5.3.2 Fish Allergens

Acknowledgement
References

6. Recent Advances in Diagnosis and Management of Shellfish Allergy
Sandip D. Kamath, Roni Nugraha and Andreas L. Lopata
6.1 Introduction
6.2 Classification of Shellfish
6.3 Prevalence of Shellfish Allergy
6.4 Clinical Manifestations and Routes of Exposure
6.5 Shellfish Allergens
6.5.1 Tropomyosin
6.5.2 Arginine kinase
6.5.3 Myosin Light Chain
6.5.4 Sarcoplasmic Calcium Binding Protein
6.5.5 Troponin C
6.5.6 Triose Phosphate Isomerase
6.5.7 Paramyosin
6.6 Clinical and Immunological Cross Reactivity
6.7 Allergy Diagnosis and Management
6.8 Food Processing and Effect on Allergens
6.9 Conclusions
Acknowledgement
References

7. Anisakis, Allergy and the Globalization of Food
Fiona J. Baird, Yasuyuki Morishima and Hiromu Sugiyama
7.1 Introduction
7.2 The Parasite
7.3 Anisakiasis: A Commonly Overlooked Infection
7.3.1 Clinical Features
7.3.2 Prevalence and Epidemiology
7.3.3 Diagnosis and Treatment
## Contents

7.3.4 Allergy and Misdiagnosis of Fish Allergy Post-Infection 164

7.4 Clinical Implications of Travelling and Globalization of Food Products on Health 167

7.5 Conclusions 169

References 170

8. Occupational Allergy and Asthma Associated with Inhalant Food Allergens 176

Mohamed F. Jeebhay and Berit Bang

8.1 Introduction—Food Industry and High Risk Working Populations 177

8.2 Food Processing Activities and Allergen Sources 178

8.3 Epidemiology and Risk Factors 183

8.4 Clinical Features and Diagnostic Approaches 189

8.5 Biological and Biochemical Characteristics of known Occupational Allergens

8.5.1 Seafood Allergens 191

8.5.2 Flour Allergens Including Enzyme Additions 193

8.5.3 Spice Allergens 194

8.6 Preventive Approaches 194

8.7 Conclusion 196

References 197

9. The Influence of Dietary Protein Modification During Food Processing on Food Allergy 203

Anna Ondracek and Eva Untersmayr

9.1 Introduction 204

9.2 Food Protein Modification: From Processing to Digestion 206

9.3 Thermal Food Processing 207

9.4 Specific Influence of Food Processing Methods on Allergenic Food Compounds

9.4.1 Peanut and Tree Nuts 209

9.4.2 Milk 212

9.4.3 Pollen Cross-reactive Food Allergens 213

9.5 Chemical Food Modification: Nitration of Dietary Proteins 214

xiii
9.6 Nitration as a Concern in Food Allergy

9.7 Further Chemical Modifications: Reduction and Oxidation of Food Proteins

9.8 Conclusions

Acknowledgements

References

10. Detection of Food Allergen Residues by Immunoassays and Mass Spectrometry

Sridevi Muralidharan, Yiqing Zhao, Steve L. Taylor and Nanju A. Lee

10.1 Introduction

10.2 Precautionary Labelling of Food Allergens

10.3 Immunoassays
  10.3.1 Enzyme-linked Immunosorbent Assay (ELISA)
  10.3.2 Non-competitive Assay for Food Analysis
  10.3.3 Competitive Inhibition ELISA
  10.3.4 Lateral Flow Devices (LFDs)

10.4 Development of an ELISA
  10.4.1 Immunogen Preparation—Tree Nut Protein Extraction and Purification
  10.4.2 Antibody Production

10.5 ELISA Optimisation
  10.5.1 Coating and Blocking
  10.5.2 Buffer System, Incubation Time and Colour Development
  10.5.3 Cross-reactivity
  10.5.4 ELISA Validation
  10.5.5 Accuracy and Precision
  10.5.6 LOD, LOQ and Detection Range
  10.5.7 Food Matrix Interference
  10.5.8 Food Processing

10.6 Mass Spectrometry for Food Allergen Detection
  10.6.1 Sample Complexity, Sample Preparation and Clean-up
  10.6.2 Allergen Detection—Intact Proteins and Complex Mixtures
  10.6.3 Detection and Quantification of Allergen Peptides/Proteins in Food Using Mass Spectrometry
### Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.6.3.1 Relative and absolute quantification of allergens</td>
<td>258</td>
</tr>
<tr>
<td>10.6.3.2 Choosing suitable ionisation source and mass analyser</td>
<td>260</td>
</tr>
<tr>
<td>10.6.3.3 Intensity and specificity of allergen signatures</td>
<td>261</td>
</tr>
<tr>
<td>10.6.3.4 Synthetic peptides and isotopic labelling</td>
<td>261</td>
</tr>
<tr>
<td>10.6.4 Food Allergen Signatures for Mass Spectrometry Based Detection</td>
<td>262</td>
</tr>
<tr>
<td>10.6.5 Effects of Food Processing on Food Allergen Detection</td>
<td>266</td>
</tr>
<tr>
<td>10.6.6 Protein Glycosylation in Food Allergens</td>
<td>266</td>
</tr>
<tr>
<td>10.6.7 Multiplexed Allergen Detection</td>
<td>268</td>
</tr>
<tr>
<td>10.7 Conclusions</td>
<td>270</td>
</tr>
<tr>
<td>References</td>
<td>271</td>
</tr>
</tbody>
</table>

### 11. Recombinant Food Allergens for Diagnosis and Therapy

*Heidi Hofer, Anargyros Roulias, Claudia Asam, Stephanie Eichhorn, Fátima Ferreira, Gabriele Gadermaier and Michael Wallner*

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.1 Introduction</td>
<td>284</td>
</tr>
<tr>
<td>11.2 Recombinant Food Allergens</td>
<td>285</td>
</tr>
<tr>
<td>11.3 Physicochemical Analysis of Recombinant Food Allergens</td>
<td>286</td>
</tr>
<tr>
<td>11.4 Immunological Analyses of Recombinant Food Allergens</td>
<td>327</td>
</tr>
<tr>
<td>11.5 Recombinant Food Allergens for Diagnosis</td>
<td>330</td>
</tr>
<tr>
<td>11.5.1 Peanut</td>
<td>332</td>
</tr>
<tr>
<td>11.5.2 Tree Nuts and Seeds</td>
<td>333</td>
</tr>
<tr>
<td>11.5.3 Fruits and Vegetables</td>
<td>334</td>
</tr>
<tr>
<td>11.5.4 Wheat</td>
<td>335</td>
</tr>
<tr>
<td>11.5.5 Soy</td>
<td>335</td>
</tr>
<tr>
<td>11.5.6 Fish</td>
<td>336</td>
</tr>
<tr>
<td>11.5.7 Shellfish</td>
<td>336</td>
</tr>
<tr>
<td>11.6 Recombinant Food Allergens for Allergy Therapy</td>
<td>337</td>
</tr>
<tr>
<td>11.7 Conclusions</td>
<td>341</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>341</td>
</tr>
<tr>
<td>References</td>
<td>342</td>
</tr>
</tbody>
</table>