Milestones in Humoral Immunity:

The history of the humoral immune system is remarkable, beginning with antibody discovery through to theories of tolerance and the surprising impact of autoantibodies on disease. Learn how immunoglobulins have driven biological discovery, diagnostics, and a new generation of targeted therapeutics.

1890: Sera transferred from immunized animals protects against tetanus & diphtheria – **Birth of serology & humoral immunity**

1896: Widal develops agglutination test to diagnose typhoid fever. First time immune response used as a diagnostic

1901: Complement fixation becomes new diagnostic
1901: First use of the term 'autoantibody'
1901: Blood types discovered

1904: First description of autoimmunity

1925: Natural antibodies discovered

1933: Histocompatibility factor proposed

1937: Tissue rejection is an immunological process in mice
1937: Serum from patients with rheumatoid arthritis acts like agglutinizing antibody
1937: Antibodies Identified as proteins

1939: IgG discovered

1940: Rheumatoid factor discovered

1941: Immunohistochemistry invented

1942: Freund's adjuvant discovered
1942: Natural antibodies react to healthy tissue

1944: IgM discovered
1944: Transplant rejection is immune mediated in humans

1945: Central tolerance theory introduced
1945: Anti-tissue antibodies found in both diseased and healthy

1946: Antibody test for syphilis identifies lupus patients

1948: Plasma cells produce antibodies
1948: Lupus erythocyte cell discovered

1953: Immunological tolerance is acquired

1954: Human leukocyte antigens (HLA) and major histocompatibility complex (MHC) described

1955: Tumor associated antibodies described in human cancer patients

1956: Autoantibodies discovered in thyroid of immunized rabbits
1956: LATS becomes first identified autoantibody

1956: Hashimoto's disease identified as autoimmune

1957: Rheumatoid arthritis identified as autoimmune
1957: Clonal selection theory described
1957: LE factor is composed of autoantibodies

1958: Scientific support for clonal selection theory

1959: New Zealand black mouse becomes first model for autoimmune diseases
1959: Clonal deletion theory proposed

1961: Thymus produces T-cells

1962: Antibody structure determined

1963: Characterization of stem cells from bone marrow

1964: Autoantibodies predate autoimmune disease
1964: First International Conference on Autoimmunity
1964: Dozens of autoantibodies identified and characterized, many non-pathological

1965: Autoantibodies described in cancer patients
1965: IgG common and variable regions sequenced
1965: Flow cytometry for cell sorting invented

1966: Autoantibodies in lupus patients pre-date symptoms

1967: Confirmation of clonal deletion theory

1968: B cells form in mammalian bone marrow
1968: B and T cells work together. Peripheral mechanisms of tolerance described

1969: Natural antibodies common in sera

1971: MHC contains the main genes that determine the risk of all autoimmune diseases
1971: ELISA developed
1971: Antibodies are polyspecific

1972: Concept of individual immunosignature born

1974: Type I diabetes identified as autoimmune
1974: Birth of recombinant DNA technology

1975: Hybridomas developed to produce monoclonal antibodies

1976: Somatic hypermutation demonstrated

1977: Ig class switching discovered

1980: Cytokine discoveries explode

1982: Islet autoantigen is first autoantigen identified
1982: CD nomenclature created
1982: Clonal anergy theory introduced

1985: Viruses can induce autoimmune disease

1986: Muromonab-CD3 first FDA approved monoclonal antibody therapy for supporting tissue transplantation
1986: Finish health study indicates RF factor present years before symptoms

1987: CTLA-4 discovered

1989: Autoantibodies appear in sets

1991: PD-1 discovered
1991: Somatic mutations occur in germinal centers

1994: Autoantibody-antigen binding conformation dependent
1994: Autoantibody screen developed for cancer targets p53 antigens

1995: Protein Microarrays become available

1997: Rituximab becomes first monoclonal antibody treatment for cancer
1997: Autoimmune regulator gene AIRE discovered

1998: Citrulline is prognostic for autoantibody pathology

2002: First autoantigen protein microarrays

2003: Autoantibodies predate lupus symptoms by years
2003: Human genome project completed

2005: Immune related adverse events identified following immune checkpoint inhibitor treatment

2007: Anti-NMDA receptor autoantibody identifies first autoimmune disease of the CNS.

2008: Array designed for cancer autoantibody detection

2009: Follicular helper T-cells drive autoimmunity

2010: Provenge becomes first autologous immunotherapy (Prostate Cancer)

2011: Immune checkpoint inhibitor Ipilimumab approved to treat metastatic melanoma

2014: Folded proteins used in microarrays

2015: Food allergy tolerance acquired in infants

2017: Kymriah – first CAR-T therapy

2018: Autoantibodies involved in immune related adverse events
2018: Machine learning applied to translational medicine

2020: COVID-19 autoantibody cross reactivity

2021: Identification of autoantigens in anti-CCP-positive and –negative rheumatoid arthritis
2021: Prognostic autoantibody biomarker panel for NSCLC
2021: Immray becomes first blood test of autoantibodies to detect pancreatic cancer (non-FDA approved)

2021: 2000% increase in liquid biopsy publications since 2008 (2,121 total).
2022: Multiple autoantibody testing for predicting progression to inflammatory arthritis

2023: Autoimmunity in Alzheimer's disease pathogenesis
2023: New autoantibody diagnostic in FDA review for Alzheimer's

2026: $97.5 Billion global biomarkers market size projected by 2026.

Harnessing The Humoral Immune Response

Over 120 years of research into the complexity and utility of the immune system set the stage for immunoprofiling. A powerful approach to biomarker discovery, endotyping and response prediction. To learn more, visit sengenics.com

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Selected References in Chronological Order

1. Kantha, S. S. (1991). A centennial review; the 1890 tetanus antitoxin paper of von Behring and Kitasato and the related developments. *Keio J Med*, *40*(1), 35-39. https://doi.org/10.2302/kjm.40.35
2. Silverstein, A. M. (1986). The Donath-Landsteiner autoantibody: The incommensurable languages of early immunologic dispute. *Cellular Immunity*, *97*(1), 16.
3. Thorsby, E. (2009). A short history of HLA. *Tissue Antigens*, *74*(2), 101-116. https://doi.org/10.1111/j.1399-0039.2009.01291.x
4. Jonsson, R. (2020). Erik Waaler (1903-1997): one of the founders of rheumatological immunology who discovered rheumatoid factor. *Ann Rheum Dis*, *79*(9), 1141-1142. https://doi.org/10.1136/annrheumdis-2019-216822
5. Silverstein, A. M. (2004). Labeled antigens and antibodies: the evolution of magic markers and magic bullets. *Nat Immunol*, *5*(12), 1211-1217. https://doi.org/10.1038/ni1140
6. Mackay, I. R. (1970). Growing points of immunology. *Postgrad Med J*, *46*(534), 182-190. https://doi.org/10.1136/pgmj.46.534.182
7. Rose, N. R. (2015). In The Beginning. *Isr Med Assoc J*, *17*(2), 74-79. https://www.ncbi.nlm.nih.gov/pubmed/26223081
8. Roitt, I. M. (2004). *Milestones in European Thyroidology: Deborah Doniach (1912-2004)*. European Thyroid Association. Retrieved 11/23/2022 from https://www.eurothyroid.com/about/met/doniach.html
9. Burnet, F. M. (1976). A modification of Jerne's theory of antibody production using the concept of clonal selection. *CA Cancer J Clin*, *26*(2), 119-121. https://doi.org/10.3322/canjclin.26.2.119
10. Tan, E. M. (1997). Autoantibodies and autoimmunity: a three-decade perspective. A tribute to Henry G. Kunkel. *Ann N Y Acad Sci*, *815*, 1-14. https://doi.org/10.1111/j.1749-6632.1997.tb52040.x
11. AAI. (2017). *The American Association of Immunologists - Interactive Timeline*. The American Association of Immunologists. Retrieved 11/17/2022 from https://www.aai.org/about/history/Interactive-Timeline
12. Morrow, J. F., et. al. (1974). Replication and transcription of eukaryotic DNA in Escherichia coli. *Proc Natl Acad Sci U S A*, *71*(5), 1743-1747. https://doi.org/10.1073/pnas.71.5.1743
13. McHugh, J. (2021). *Autoantibodies emerge on the scene*. Nature. Retrieved 11/29/2022 from https://www.nature.com/articles/d42859-021-00010-5
14. *The HLDA Workshops*. (2022). HCDM. Retrieved 12/12/2022 from https://hcdm.org/index.php?option=com_content&view=category&layout=blog&id=13&Itemid=105
15. *FDA Approval Timeline of Active Immunotherapies*. (2021, 9/7/2022). Retrieved 10/31/2022 from https://www.cancerresearch.org/fda-approval-timeline-of-active-immunotherapies
16. Bizzaro, N. (2007). Autoantibodies as predictors of disease: the clinical and experimental evidence. *Autoimmun Rev*, *6*(6), 325-333. https://doi.org/10.1016/j.autrev.2007.01.006
17. Barnes, K. (2018). The first monoclonal antibody therapy. *Nature Research*. https://doi.org/10.1038/d42859-018-00024-6
18. Muro, Y., et. al. (1994). Synthetic compound peptide simulating antigenicity of conformation-dependent autoepitope. *J Biol Chem*, *269*(28), 18529-18534. https://www.ncbi.nlm.nih.gov/pubmed/7518436
19. Schena, M., et. al. (1995). Quantitative monitoring of gene expression patterns with a complementary DNA microarray. *Science*, *270*(5235), 467-470. https://doi.org/10.1126/science.270.5235.467
20. Robinson, W. H., et. al. (2002). Autoantigen microarrays for multiplex characterization of autoantibody responses. *Nat Med*, *8*(3), 295-301. https://doi.org/10.1038/nm0302-295
21. Arbuckle, M., et. al (2003). Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N Engl J Med*, *349*(16), 1526-1533. https://doi.org/10.1056/NEJMoa021933
22. Dalmau, J., et. al. (2007). Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol*, *61*(1), 25-36. https://doi.org/10.1002/ana.21050
23. Schiaffino, M. T., et. al. (2020). Immunoserologic Detection and Diagnostic Relevance of Cross-Reactive Autoantibodies in Coronavirus Disease 2019 Patients. *J Infect Dis*, *222*(9), 1439-1443. https://doi.org/10.1093/infdis/jiaa485
24. Patel, A. J., Tan, T. M., Richter, A. G., Naidu, B., Blackburn, J. M., & Middleton, G. W. (2022). A highly predictive autoantibody-based biomarker panel for prognosis in early-stage NSCLC with potential therapeutic implications. *Br J Cancer*, *126*(2), 238-246. https://doi.org/10.1038/s41416-021-01572-x
25. Chatanaka, M. K., et. al. (2023). Beyond the amyloid hypothesis: how current research implicates autoimmunity in Alzheimer's disease pathogenesis. *Crit Rev Clin Lab Sci*, 1-29. https://doi.org/10.1080/10408363.2023.2187342