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**DEPARTEMENT OF BIOTECHNOLOGY**

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# DISSERTATION

Presented by

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**BOUCHENINE NARIMENE**

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# MASTER

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**TOPIC**

# Particulate adjuvants for therapeutic uses

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# *Dedication*

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*We hope this autobiography serves as a sincere tribute to the enduring love that unites us, the timeless wisdom passed down through generations, and the sacred bond that holds our family close.*

*Through this love this cherished legacy we find the strength to endure life's hardships, to rise stronger after every fall, and to shape our journey with grace, courage, and a deep sense of belonging that time cannot erase.*

*NARIMÈNE*

## ***Dedication***

*First of all, I would like to thank God Almighty for his grace and generosity that enabled me to complete this work and i would like to thank myself for believing in me and for not giving up even in the difficult moments.*

*I dedicate the fruit of my success to those who gave me life, to the light that guides me in the darkness, to those who have supported me in every step of my life:*

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*To those who have left this life but are still exist in our minds.*

*Finally, to everyone who has a special place in my heart and everyone who has had an impact on my life.*

*SALSABIL*

# LIST OF ABBREVIATIONS

**CFA**: Complete Freund's Adjuvant.

**DTP**: Diphtheria, Tetanus, Pertussis.

**HPV**: Human Papillomavirus.

**HIB**: Haemophilus Influenzae Type B.

**IFA**: Incomplete Freund's Adjuvant.

**VLP**: Virus-Like Particle.

**APCs**: Antigen-Presenting Cells.

**NA**: Neuraminidase.

**HA**: Hemagglutinin.

**PLA**: Polylactic Acid.

**PLGA**: Poly(lactic-co-glycolic acid).

**TLRs**: Toll-Like Receptors.

**AS01**: Adjuvant System 01.

**AS02**: Adjuvant System 02.

**AS04**: Adjuvant System 04.

**TH1**: T Helper 1.

**TH2**: T Helper 2.

**PAMPs**: Pathogen-Associated Molecular Patterns.

**DAMPs**: Damage-Associated Molecular Patterns.

**CTLs**: Cytotoxic T Lymphocytes.

**LPS**: Lipopolysaccharide.

**BCG**: Bacillus Calmette–Guérin.

**SSRNA**: Single-Stranded Ribonucleic Acid.

**TB**: Tuberculosis.

**TNFRSF17**: Tumor Necrosis Factor Receptor Superfamily Member 17.

**MF59:** MicroFluidized Squalene-Based Emulsion Adjuvant.

**AIT**: Allergen Immunotherapy.

**SCIT**: Subcutaneous Immunotherapy.

**SLIT**: Sublingual Immunotherapy.

**CpG**: Cytosine-phosphate-Guanine Oligodeoxynucleotide.

**DDT**: Dichloro-Diphenyl-Trichloroethane (Note: pesticide, not immune-specific but sometimes found in research context).

**KLH**: Keyhole Limpet Hemocyanin.

**AD**: Atopic Dermatitis (contextual; could also be Alzheimer's Disease).

**IOE**: Immunoglobulin E Overexpression (or Institute of Epidemiology depending on context)

**ISA**: Immuno-Stimulating Adjuvant (also known in SEPPIC formulations).

**RAS**: RIBI adjuvant System.

**CWS**: Cell Wall Skeleton.

**MPL**: Monophosphoryl Lipid A.

**CW**: Cell Wall.

**SAF**: System adjuvants formulation.

**NCI**: National Cancer Institute.

**FU**: Follow-Up (or 5-Fluorouracil in oncology).

**VBM**: Vaccine-Based Modulation (or Voxel-Based Morphometry in neuroimaging).

**HER2**: Human Epidermal Growth Factor Receptor 2.

**CMF**: Cyclophosphamide, Methotrexate, Fluorouracil (chemotherapy regimen).

**ER**: Estrogen Receptor.

**NOD**: Nucleotide-binding Oligomerization Domain (or Non-Obese Diabetic depending on context).

**ODN**: Oligodeoxynucleotide.

**ALUM**: Aluminum Salts (usually Aluminum Hydroxide or Aluminum Phosphate).

**MHC I**: Major Histocompatibility Complex Class I.

**CTLs**: Cytotoxic T Lymphocytes (repeated).

**ISCOMS** : Immune Stimulating Complexes.

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## Abstract:

This manuscript explores the crucial role of adjuvants—substances used to enhance the effectiveness of pharmaceuticals such as vaccines, antibiotics, antibodies, and chemotherapy. Adjuvants are classified into two main types: delivery systems (e.g., aluminum salts, emulsions, microparticles) and immunostimulants (e.g., TLR and NOD receptor agonists), which help activate and direct the immune response. The study highlights the adjuvants use in overcoming bacterial resistance (e.g., clavulanate, avibactam), improving the efficacy of therapeutic vaccines for complex diseases like cancer and Alzheimer's (e.g., MF59, AS04), stimulating antibody production in animals (e.g., FCA), and enhancing chemotherapy after surgery to reduce relapse risks. Despite their effectiveness, adjuvants still face challenges related to cost and side effects, underlining the need for safer, more targeted, and accessible alternatives in the future of medical treatments.

**Key words:** pharmaceutical adjuvants, immunostimulants, delivery enhancement, precise targeting.

## الملخص

يتناول هذا البحث دور المواد المُساعدة وأهميتها في تعزيز فعالية العلاجات الطبية مثل اللقاحات، والمضادات الحيوية، والأجسام المضادة، والعلاج الكيميائي. تصنف المواد المساعدة إلى نوعين رئيسيين: أنظمة التوصيل (مثل أملاح الألمنيوم والمستحلبات والجزيئات الدقيقة) والمنشّطات المناعية (مثل محفزات مستقبلات TLR و(NOD، والتي تعمل على تنشيط الاستجابة المناعية وتوجيهها. ويستعرض البحث استخدام هذه المواد في مكافحة المقاومة البكتيرية (مثل الكلافولانات والأفيباكتام)، وفي تحسين فعالية اللقاحات العلاجية ضد أمراض معقدة مثل السرطان والزهايمر مثل ( 59MF و 04AS)، وكذلك في تحفيز إنتاج الأجسام المضادة في الحيوانات (مثلFCA)، وأخيرًا في دعم فعالية العلاج الكيميائي بعد العمليات الجراحية لتقليل خطر الانتكاس. ورغم فعاليتها، ما تزال هذه المواد تُواجه تحديات تتعلق بالتكلفة والآثار الجانبية، مما يؤكد الحاجة إلى تطوير مواد مساعدة أكثر أمانا ودقة وتوفًّرا في المستقبل

**الكلمات المفتاحية:** السواغات الصيدلانية، محفزات المناعة، تعزيز التوصيل، الاستهداف الدقيق.

## Résumé:

Ce mémoire analyse le rôle essentiel des adjuvants, des substances qui renforcent l’efficacité de divers traitements médicaux comme les vaccines, les antibiotiques, les anticorps et la chimiothérapie. Il examine leur classification en deux grandes catégories : les systèmes de délivrance (sels d’aluminium, émulsions, microparticules) et les immunostimulants (agonistes TLR, NOD), qui permettent d’activer et d’orienter la réponse immunitaire. Leur utilisation est détaillée dans plusieurs domaines : en antibiothérapie pour surmonter la résistance bactérienne (ex:clavulanate, avibactam), en vaccination pour améliorer l’immunogénicité et développer des vaccines thérapeutiques (ex. : MF59, AS04), en production d’anticorps chez l’animal (ex:FCA), ainsi qu’en chimiothérapie pour augmenter l’efficacité des traitements post-opératoires et réduire les risques de rechute. Bien qu’efficaces, les adjuvants posent encore des problèmes de coût et de tolérance, soulignant la nécessité de développer des alternatives plus sûres, accessibles et ciblées pour un meilleur avenir thérapeutique.



**Mots-clés:** adjuvants pharmaceutiques, immunostimulants, amélioration de la délivrance, ciblage précis.