BIA-ALCL

TGA update 25.7.18

Professor

Surgical Infection Research Group, Macquarie University
Integrated Specialist Healthcare Education and Research Foundation
Sydney Australia

Integrated Specialist Healthcare
Education & Research Foundation

MACQUARIE
University

BIA-ALCL

[redacted].

DISCLOSURES

ALLERGAN research coordinator, consultant

[redacted] research coordinator, consultant

[redacted] research coordinator, consultant

[redacted] educator, consultant

[redacted] contract research

BIA-ALCL

[redacted]

COI for	[redacted]

[redacted]

5. How many breast implant companies are you engaged with currently	4

[redacted]

10. Do you have any personal cases of BIA-ALCL arising from your personal practice and if so how many?	N

[redacted]

I certify that the statements and information are true, accurate and complete.

[redacted]

BIA-ALCL - FACTS

- It is a cancer (WHO)
- It occurs in association with breast implants*
- All patients have been exposed to textured implants
- High surface area implants are associated with 14-18x higher risk of disease (1 in 3-5k vs 1 in 60k)
- It takes between 7-9 years to develop
- It can occur in both reconstructive and aesthetic cases
- Most commonly presents with late seroma
- Less commonly presents with mass/spread which carries worse prognosis
- Its detection and incidence is increasing
- There are significant racial and geographic variations

BIA-ALCL - WHAT WE THINK WE KNOW

- Implant specific risk
- Aetiopathogenesis
  - Unifying hypothesis vs particles vs friction vs silicone toxicity
  - Lymphomagenesis and the transformation of T cells
- Stage 1a disease - indolent and confined to seroma and risk of progressive disease

[redacted]

BIA-ALCL - WHAT WE STILL DON’T KNOW

- Spectrum with LPD?
- Why is there racial/geographic variation?
- Under reporting : cost vs legal liability?
- Genetic / HLA predisposition

ANZ EPIDEMIOLOGY PAPER PUBLISHED IN OCT PRS

BREAST [redacted]

- Unprecedented 4 expert commentaries
- Implant specific risk calculated for defined numerator and denominator for 3 implant types
- Risk for high surface area textured implants is quantified - high surface area texture has risk of around 1 in 3800 implants [redacted]
- Clarity of why some implants are more associated with BIA-ALCL

Breast Implant–Associated Anaplastic Large Cell Lymphoma in Australia and New Zealand: High-Surface-Area Textured Implants Are Associated with Increased Risk

[redacted]

Special update : the epidemiology of breast implant associated anaplastic large cell lymphoma in Australia and New Zealand confirms th highest risk for grade 4 surface breast implants

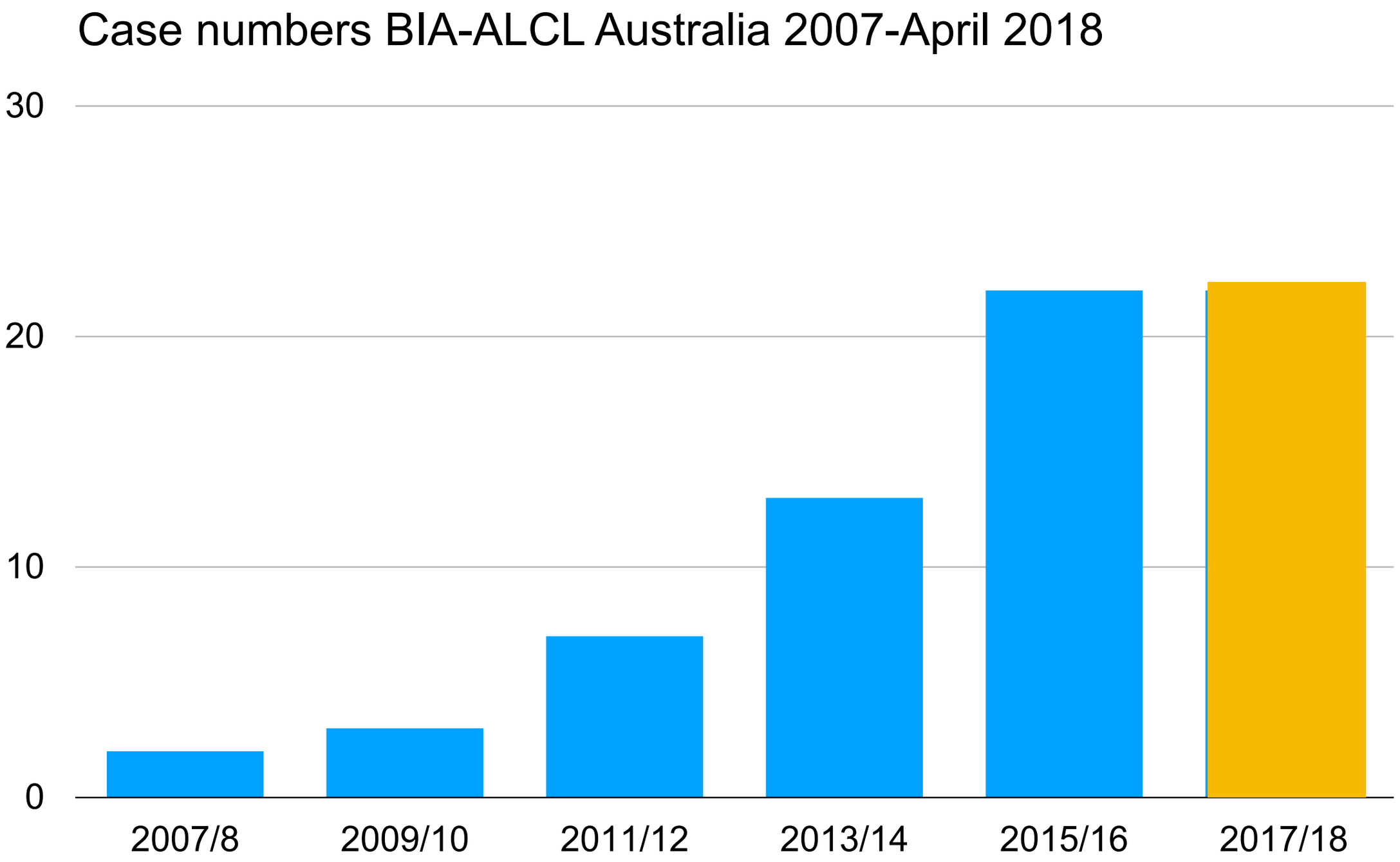
ASPS/ASAP BIA ALCL task force, NZ Association of Plastic Surgeons, Breast Surgeons Australia & New Zealand, Australian Breast Device Registry, Sir Peter MacCallum Cancer Centre, Macquarie University and ISHCERF

PRS under review

Integrated Specialist Healthcare
Education & Research Foundation

MACQUARIE University

RISK


Case numbers BIA-ALCL Australia 2007-April 2018
30
20
10
0
2007/8
2009/10
2011/12
2013/14
2015/16
2017/18

UPDATED AUSTRALIAN NUMBERS - APRIL 2018

- 72 Confirmed in Australia (up from 44 in December 2016)
- 13 confirmed in NZ (up from 9 in December 2016)
- 54% increase in newly diagnosed cases
- 2 more being worked up
- Prospective collection of implants, samples, genetics and tumour as well as clinical data thanks to Unified Collection form

The functional influence of breast implant outer shell morphology on bacterial attachment & growth

Surgical Infection Research Group, Macquarie University
Integrated Specialist Healthcare Education and Research Foundation
Australia Center for Microscopy and Microanalysis University of Sydney
University of Texas, Southwestern, Monash University

PRS in press

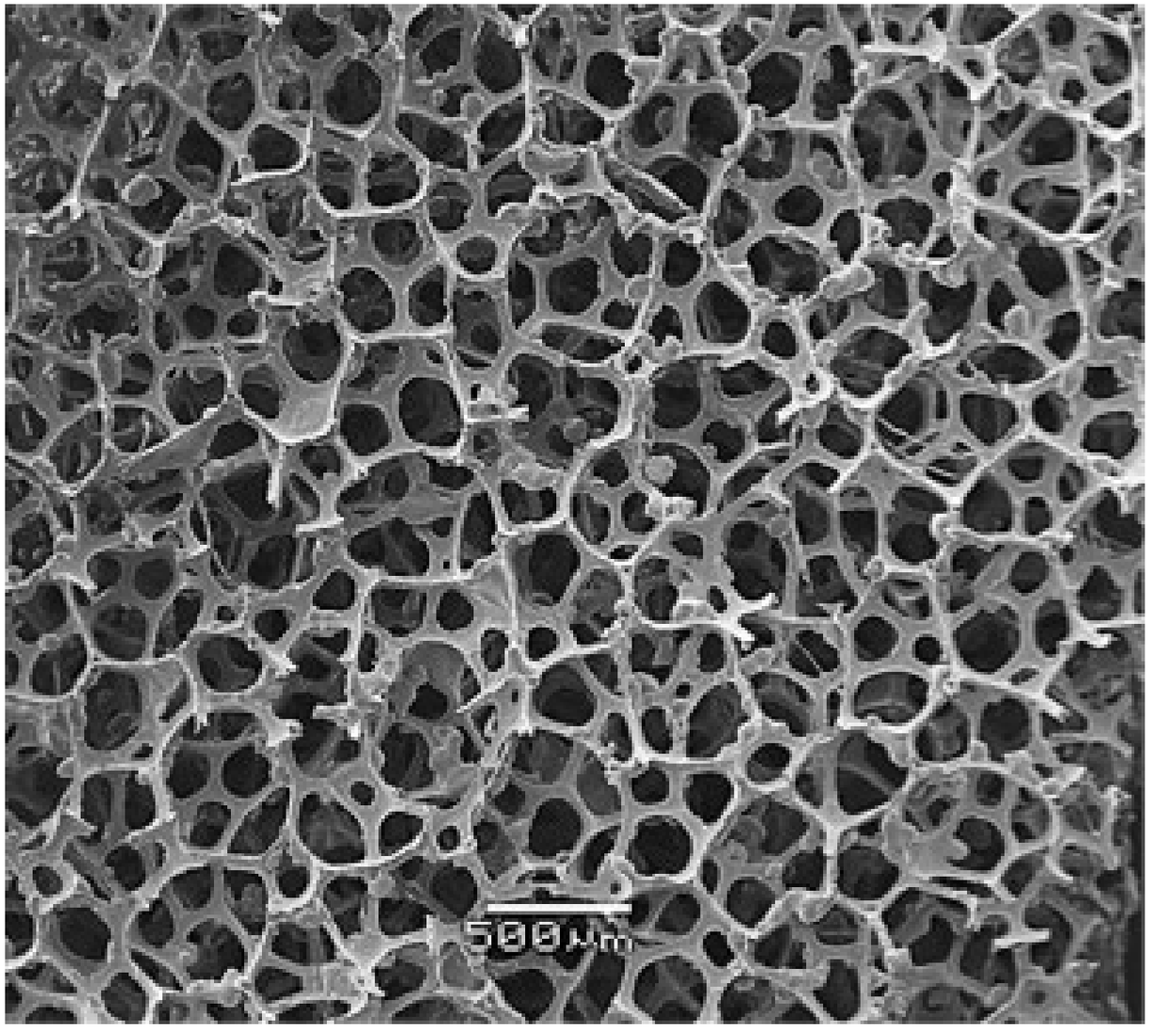
Integrated Specialist Healthcare
Education & Research Foundation

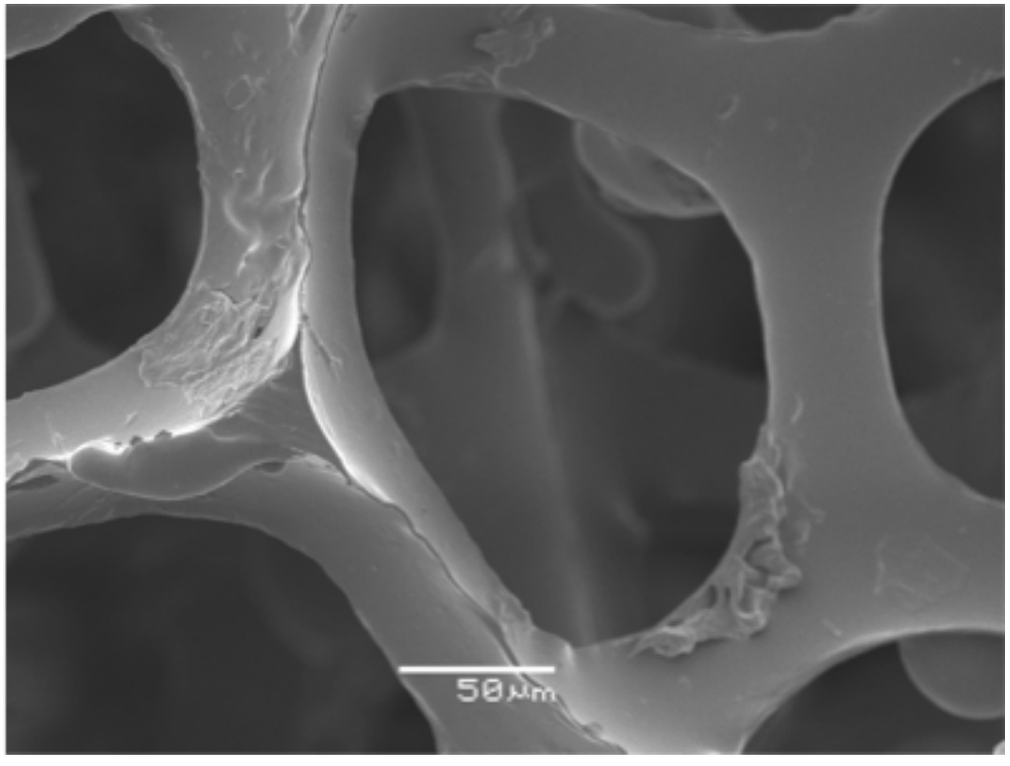
MACQUARIE University

IMPLANT SURFACE

[redacted].

SEM

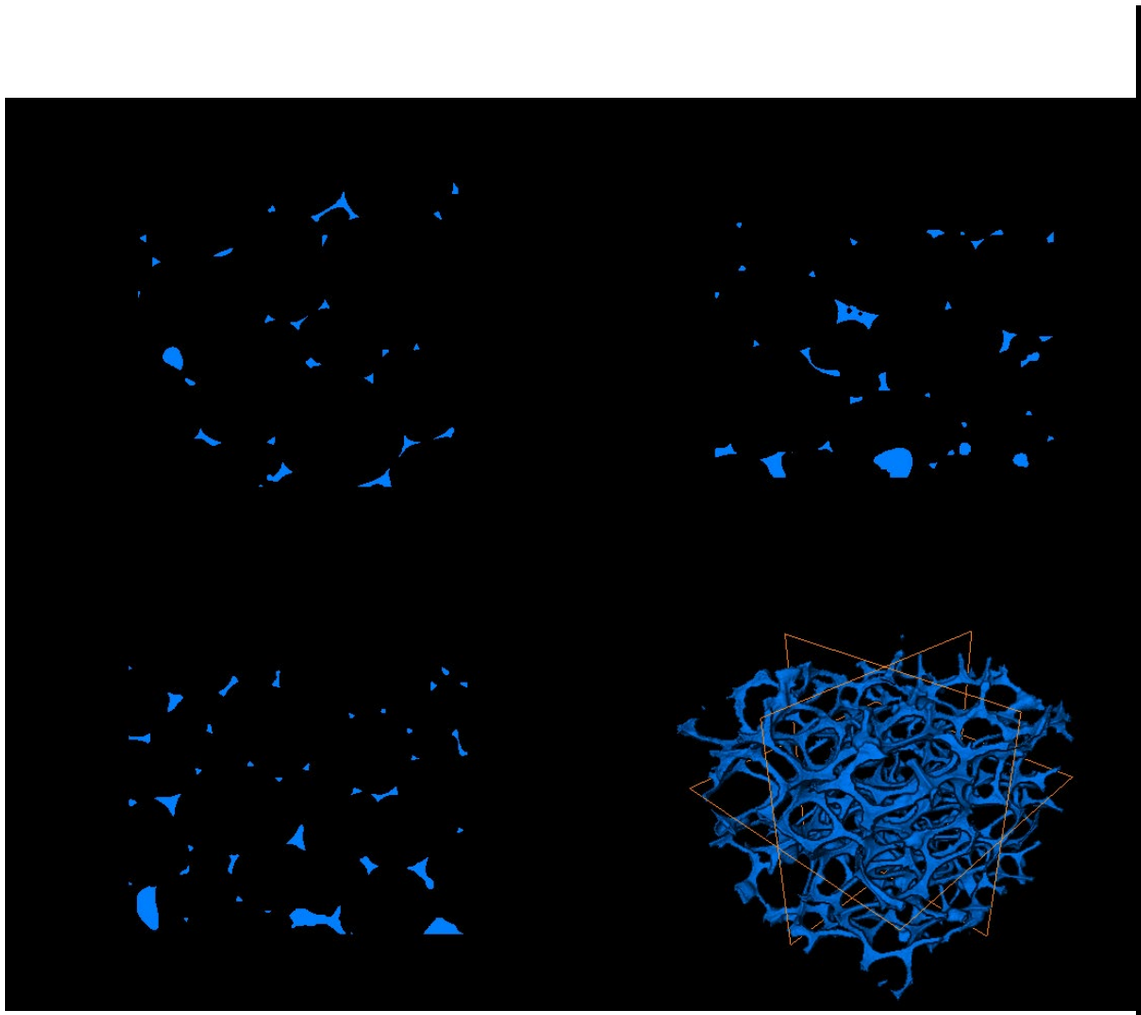


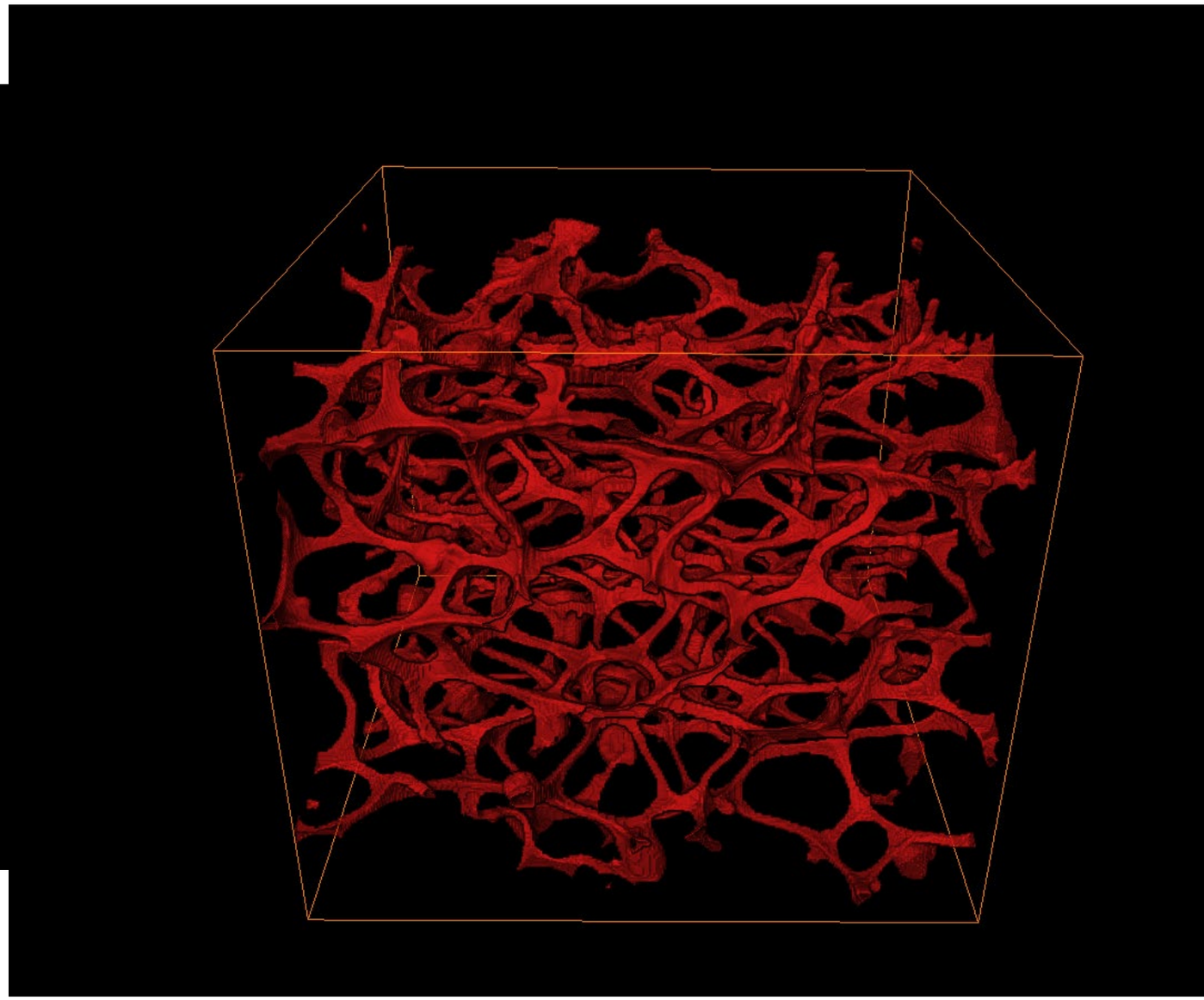


[redacted] POLYURETHANE

[redacted]

3D reconstructions





[redacted] POLYURETHANE

SURFACE GRADE VS TEXTURE/SMOOTH

Process	Polyurethane foam	Salt Loss (Biocell/ Eurosilicone)	Gas Diffusion	Salt Loss (Nagotex)	Imprinting	Smooth/Nano
Surface Area	High	Intermediate	Intermediate	Low	Low	Minimal
Roughness	High	Intermediate	Low	Low	Low	Minimal
SURFACE TYPE	4	3	3	2	2	1

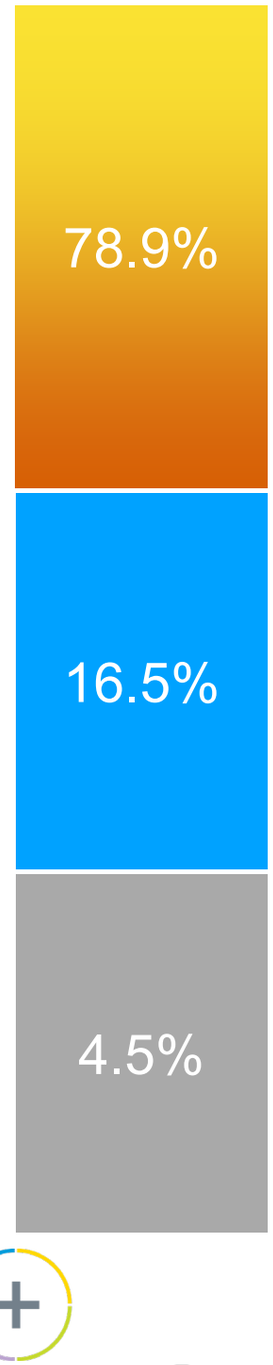
BIA-ALCL

[redacted]

RISK

UPDATED IMPLANT DATA (N=110) APRIL 2018

Manufacturer	Texture name	SA/SR	Grade	No.	%
[redacted]	Polyurethane	High	4	23	21.1
[redacted]	Polyurethane	High	4	1	0.9
[redacted]	Polyurethane	High	4	1	0.9
[redacted]	[redacted]	Intermediate	3	61	56.0
[redacted]	Nagotex (salt loss)	Low	2	7	6.4
[redacted]	Siltex	Low	2	7	6.4
[redacted]	PIP	Low	2	4	3.7
[redacted]	Smooth	Minimal	1	3	1.8
Unknown	Smooth	Minimal	1	2	1.8
Unknown	Texture	?	?	1	0.9



CLINICOPATHOLOGICAL STAGING N=81

Clinical	TNM	Stage	No	%	Mortality
Tumor positive in seroma capsule negative	T1N0M0	1A (neg)	51	62.9	-
Tumor positive in seroma and inner lining of capsule	T1N0M0	1A (pos)	13	16.0	-
Tumor infiltrating capsule	T3N0M0	1C	6	7.4	-
Mass beyond capsule	T4N0M0	2A	9	11.1	2
Mass with single axillary met	T4N1M0	3	1	1.2	1
Mass with multiple axillary mets	T4N2M0	3	1	1.2	1

[redacted]

[redacted]

Aetiopathogenesis

UNIFYING HYPOTHESIS - BIA-ALCL ([redacted]

Host (Genetic factors)

T lymphocyte

Polyclonal proliferation

Monoclonal proliferation

Bacterial antigenic stimulation

Biofilm

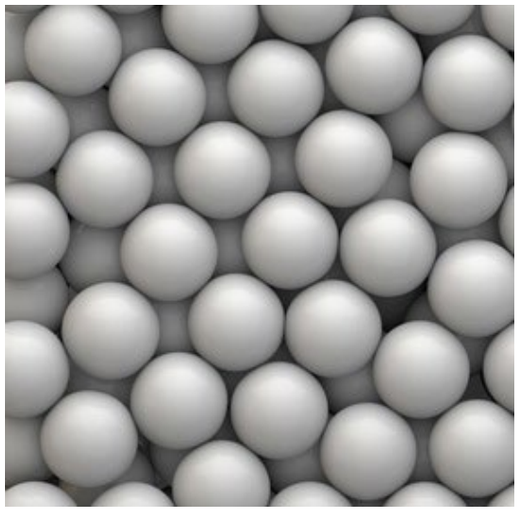
Breast implant

BIA-ALCL

Aetiopathogenesis

ALTERNATIVE SOURCES OF INFLAMMATION

FRICTION



SILICONE PARTICLES

ALLERGIC INFLAMMA
(HEAVY METALS, TOXICITY)

Aetiopathogenesis

WHY BACTERIAL ANTIGENS ARE FIRMING UP

- Lymphomagenesis vs Carcinogenesis
- Textured implants, surface area and lymphocyte stimulation
- Bacterial Infection leading to Cancer/Lymphoma
- Epidemiology - clusters
- Primary cutaneous ALCL
- ALCL microbiome
- Microbiome and Carcinogenesis

Aetiopathogenesis

INFECTION - LYMPHOMA

Table 1. World Health Organization classification lymphoma subtypes associated with infections

Microbial pathogen	World Health Organization (WHO) histologic subtype
Human T-lymphotropic virus 1 (HTLV-1)	Adult T-cell leukemia/lymphoma
Human immunodeficiency virus (HIV)	Hodgkin disease (with EBV)
	Burkitt lymphoma (with or without EBV)
	DLBCL (including primary effusion lymphoma and plasmablastic lymphoma)
	Extranodal MZ lymphoma, MALT-type (rare)
	T-cell lymphoma (rare)
Epstein-Barr virus (EBV)	Hodgkin disease
	Polymorphic PTLD
	Burkitt lymphoma
	Monomorphic PTLD (DLBCL)
	Primary effusion lymphoma (with HHV8)
Human herpesvirus 8/Kaposi sarcoma-associated herpesvirus (HHV8/KSHV)	Primary effusion lymphoma
	Plasmablastic lymphoma (DLBCL)
	PTLD (rare)
Hepatitis C virus (HCV)	SLVL (splenic MZ lymphoma)
	Other marginal zone lymphoma
	DLBCL
Helicobacter pylori	Gastric MALT lymphoma (extranodal MZ lymphoma, MALT-type)
Campylobacter jejuni	IPSID (extranodal MZ lymphoma, MALT-type)
Borrelia burgdorferi	Primary cutaneous B-cell lymphoma (various WHO subtypes including extranodal MZ lymphoma, MALT-type)
Chlamydia psittaci	Ocular adnexal lymphoma (extranodal MZ lymphoma, MALT-type)

DLBCL indicates diffuse large B-cell lymphoma; MZ, marginal zone; MALT, mucosa-associated lymphoid tissue; PTLD, posttransplantation lymphoproliferative disorder; SLVL, splenic lymphoma with villous lymphocytes; and IPSID, immunoproliferative small intestinal disease.

BIA-ALCL

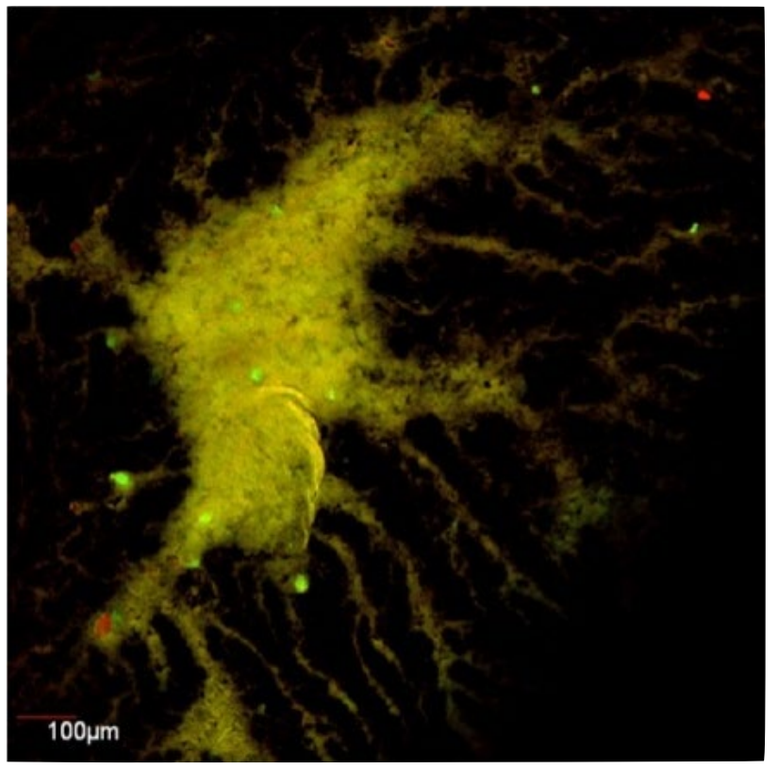
[redacted]

Aetiopathogenesis

TEXTURED IMPLANTS, BACTERIA, LYMPHOCYTES

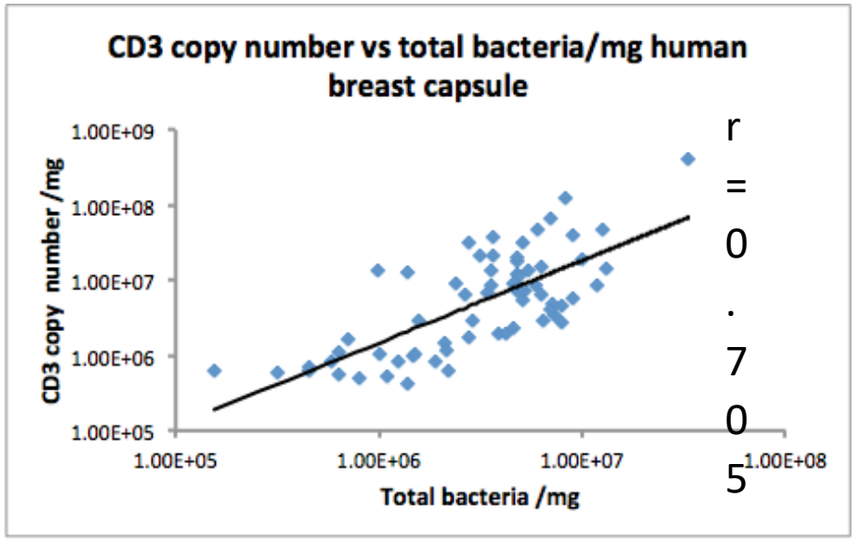
In Vitro and In Vivo Investigation of the Influence of Implant Surface on the Formation of Bacterial Biofilm in Mammary Implants

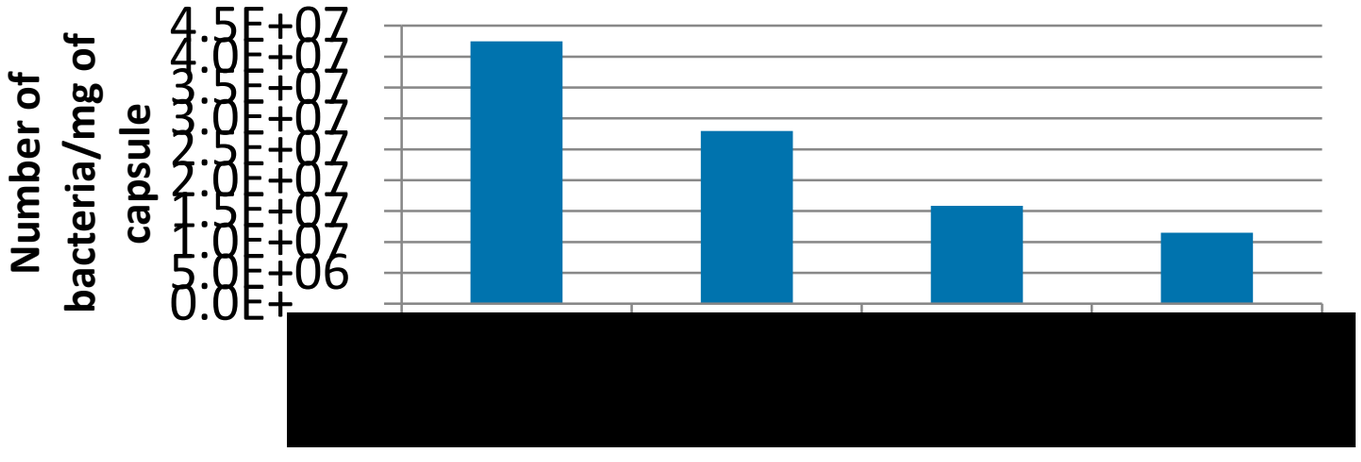
[redacted]



Chronic Biofilm Infection in Breast Implants Is Associated with an Increased T-Cell Lymphocytic Infiltrate: Implications for Breast Implant–Associated Lymphoma

[redacted]





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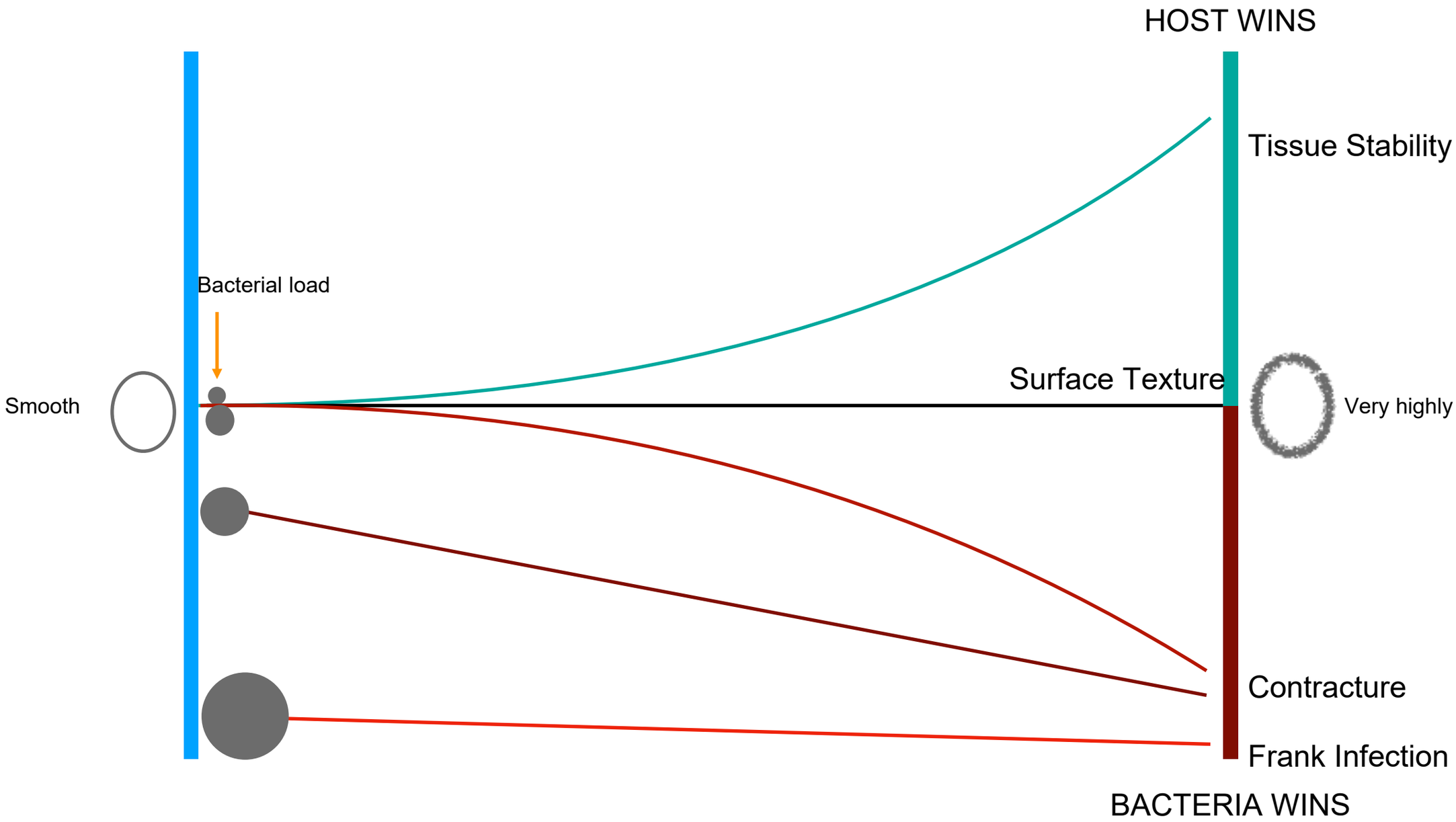
Aetiopathogenesis

RACE TO THE SURFACE

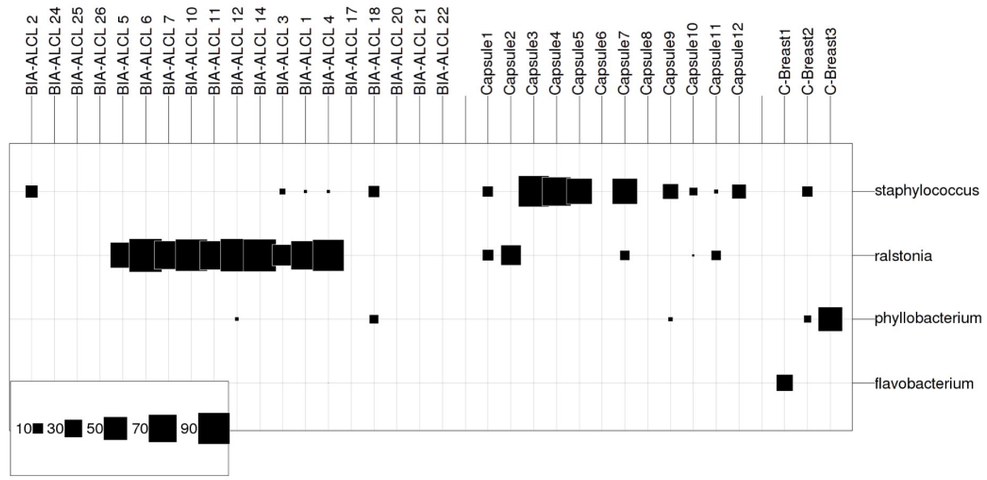


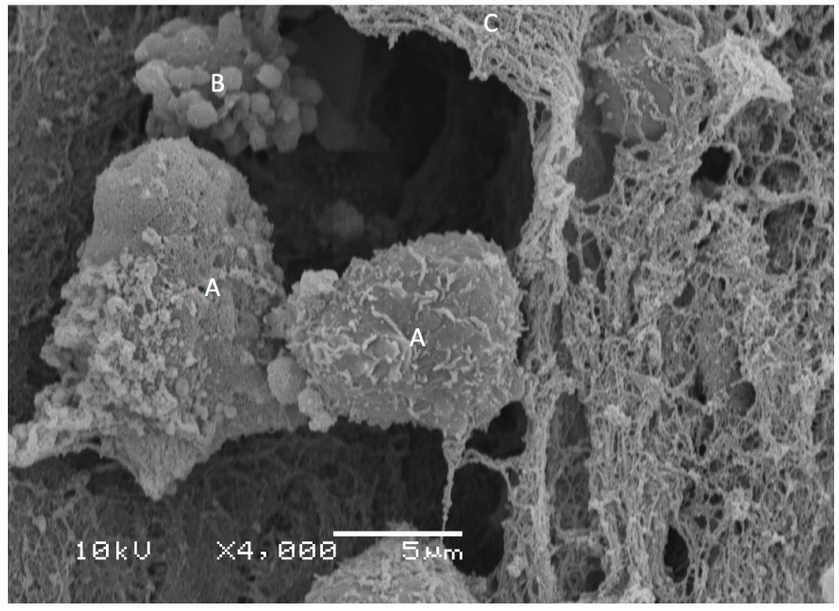
BACTERIA IN BIA-ALCL

- High level of bacterial presence analogous to Grade IV contracture
- Gram negative microbiome in BIA-ALCL
- Prospective study ongoing showing consistency in gram -ve shift
- Investigating tumour response to bacterial (and other antigens)

Bacterial Biofilm Infection Detected in Breast Implant–Associated Anaplastic Large-Cell Lymphoma

[redacted]





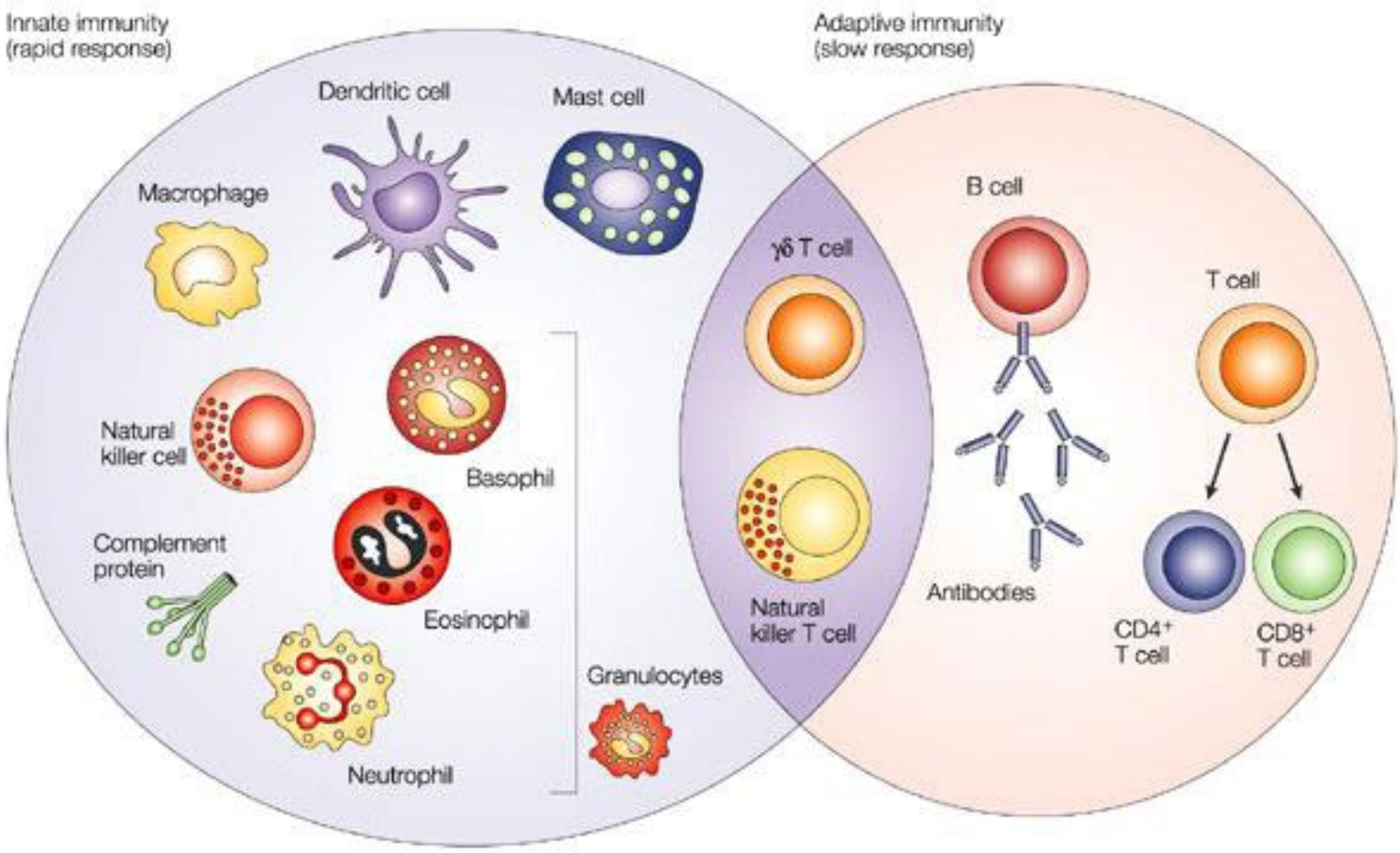
Winner James Barrett Brown Award 2017

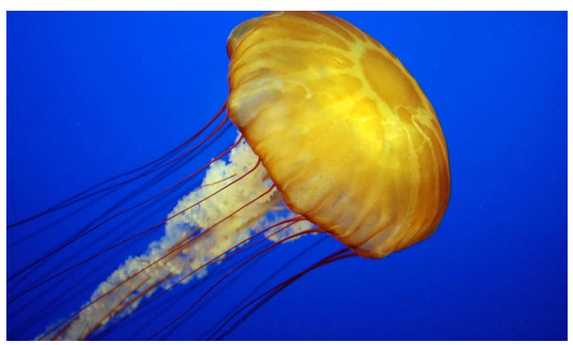
EPIDEMIOLOGY - CLUSTERS

- Cluster patterns of incidence - single surgeon between 2-8 cases
- Seen in other series
- Study of clusters (where surgeon is cooperating) - water contamination, variation in infection control, genetic sampling
- Ongoing investigation - Findings to be published 2018
- Why are we seeing it now - textured implants and better technique have lead to longer life of implants in patients and less re-operation = BIA-ALCL
- Cosmetic incidence higher - patients are younger and less reoperation

Aetiopathogenesis

INNATE (NON SPECIFIC) VS ADAPTIVE IMMUNITY





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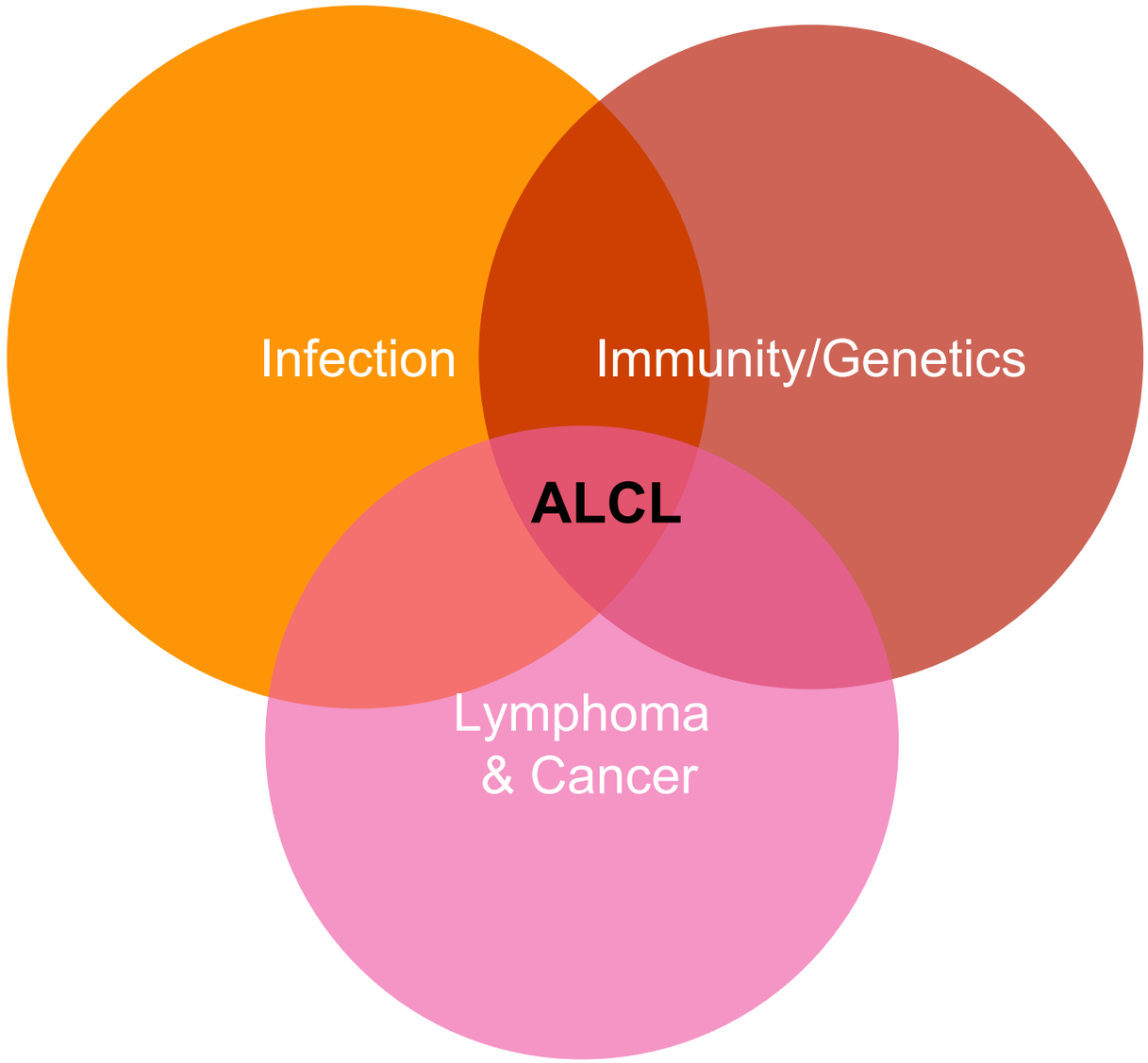
Aetiopathogenesis

CARCINOGENESIS VS LYMPHOMAGENESIS

T cell Lymphoma is caused by biological antigen e.g. bacteria, autoimmunity (Sjogrens), gluten, immunosuppression interacting with progenitor lymphocyte



Differential mitogenic response of breast implant associated anaplastic large cell lymphoma to gram negative lipopolysaccharide (LPS) is mediated through Toll like receptor 4 pathway - a novel pathway for bacterial pathogenesis of malignancy

Surgical Infection Research Group, Macquarie University, Boston University
Integrated Specialist Healthcare Education and Research Foundation
Peter MacCallum Cancer Cancer Center and Epworth Healh
University of Texas, Southwestern, Monash University

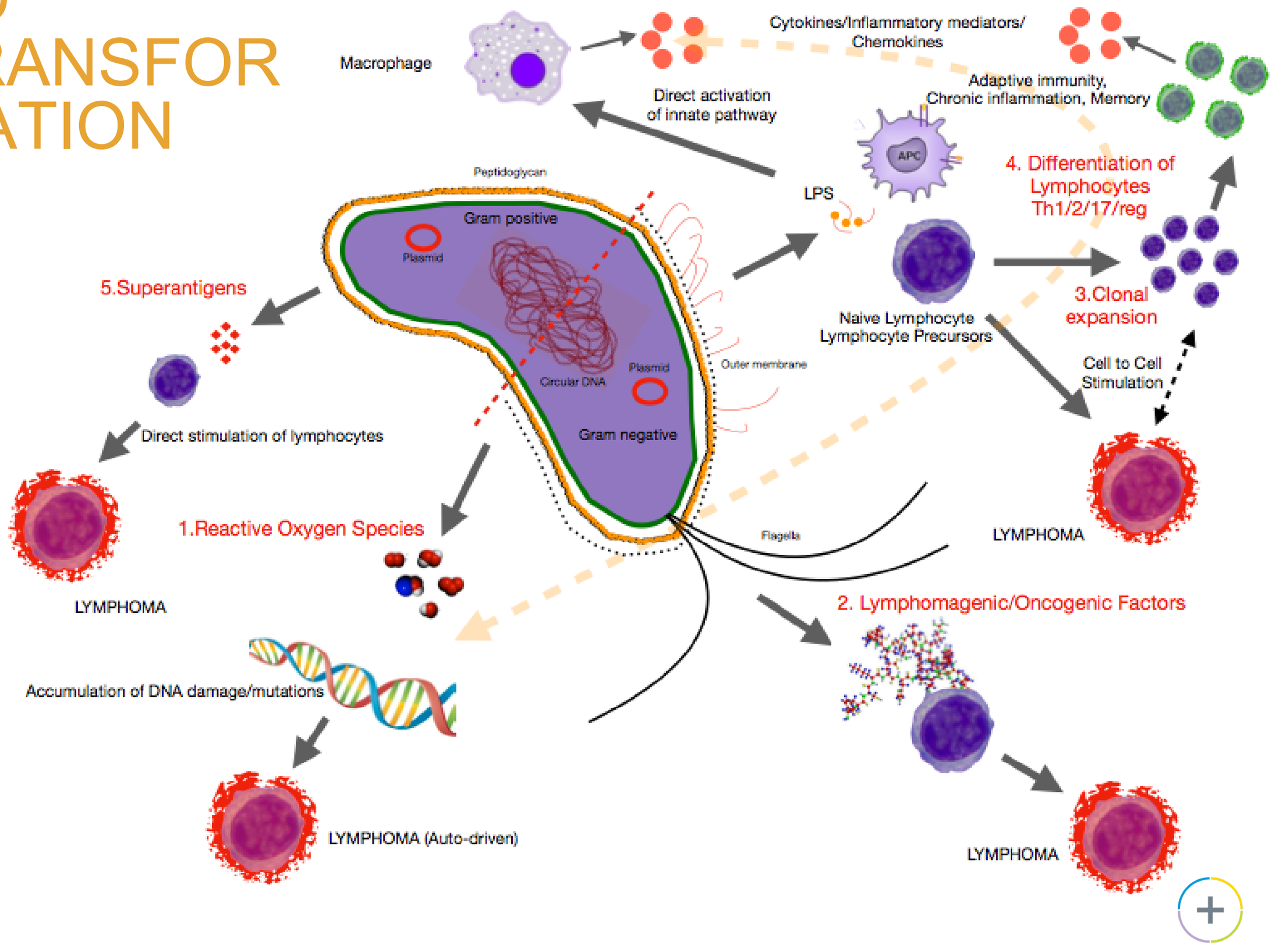
Integrated Specialist Healthcare
Education & Research Foundation

MACQUARIE University

BIA-ALCL

[redacted]THWAYS TO TRANSFOR MATION

Aetiopathogenesis



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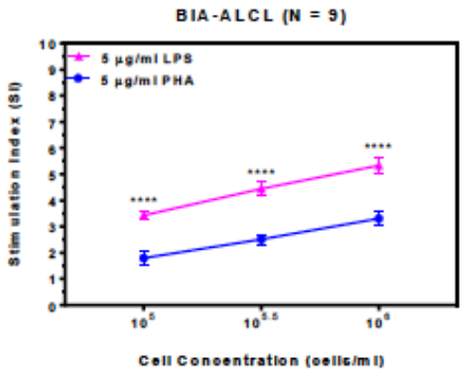
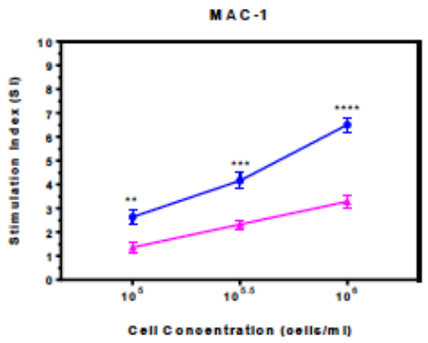
Aetiopathogenesis

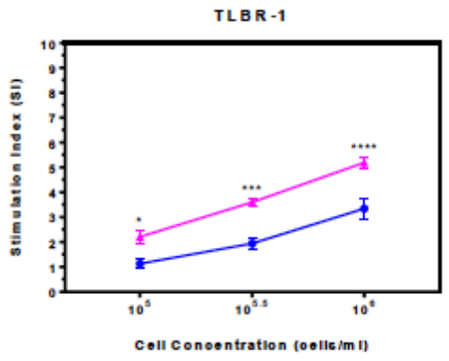
LPS PRODUCES UNIQUE PROLIFERATION OF BIA-ALCL TUMOUR CELLS

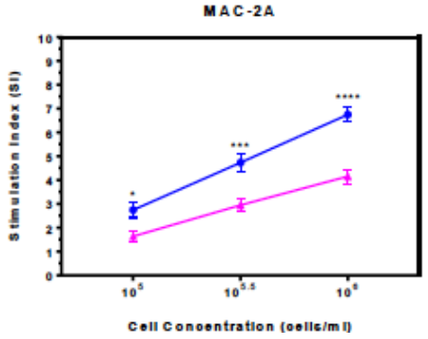
BIA-ALCL and Tumour Cell Lines

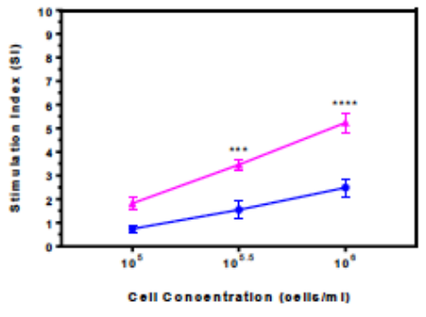


PC - ALCL

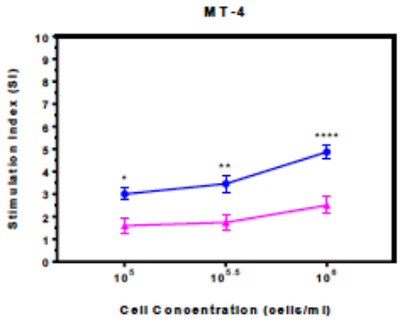


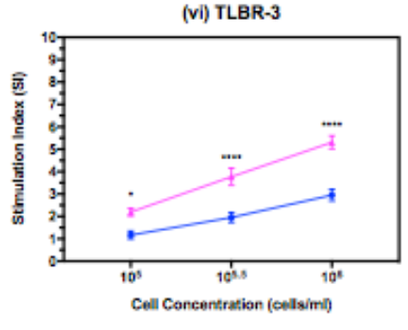






Immortal T cell line

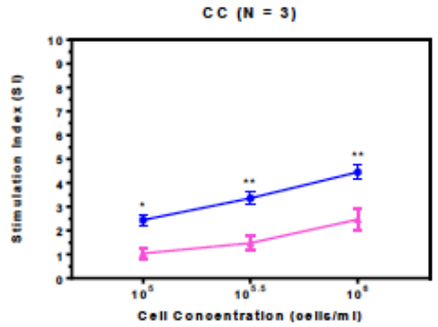




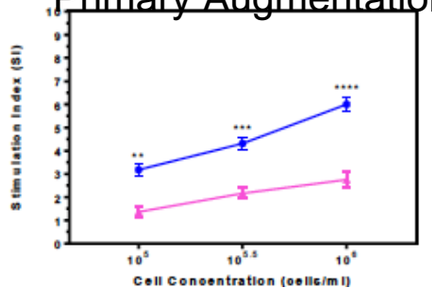
LPS

PHA

Capsular Contracture



Primary Augmentation



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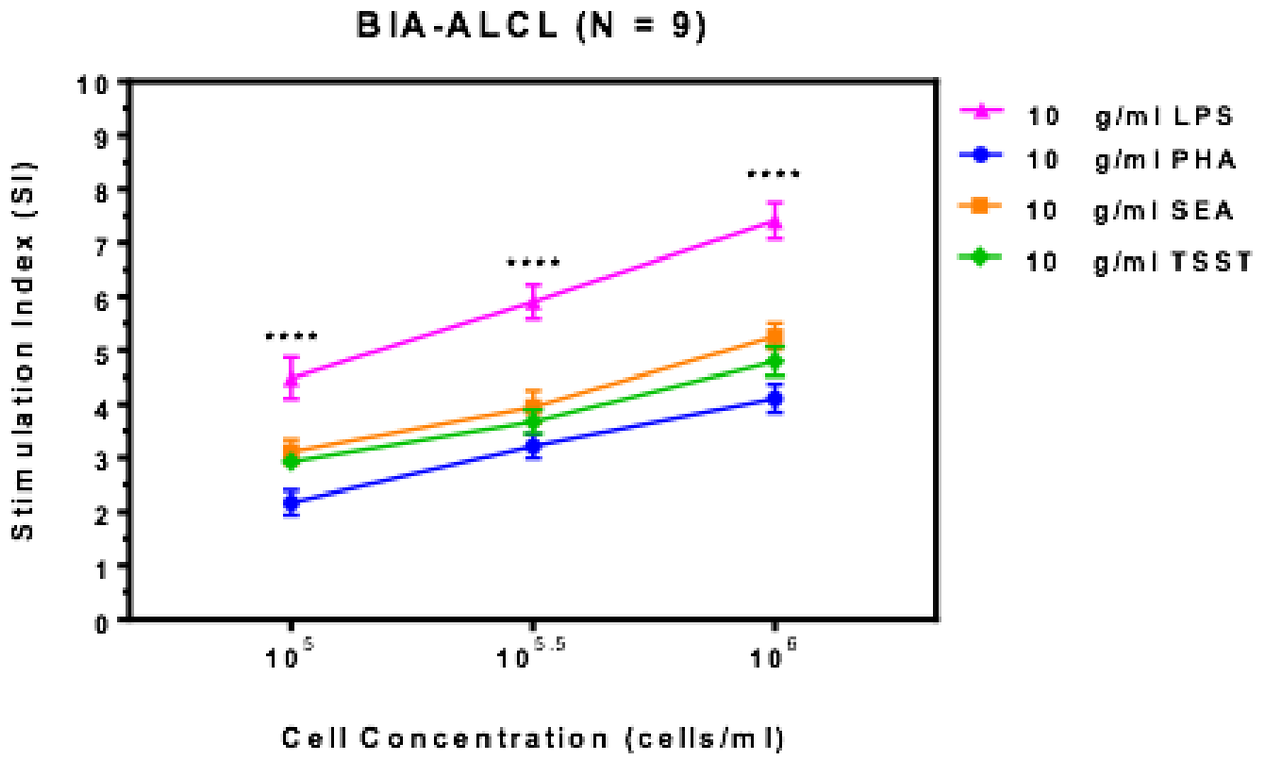
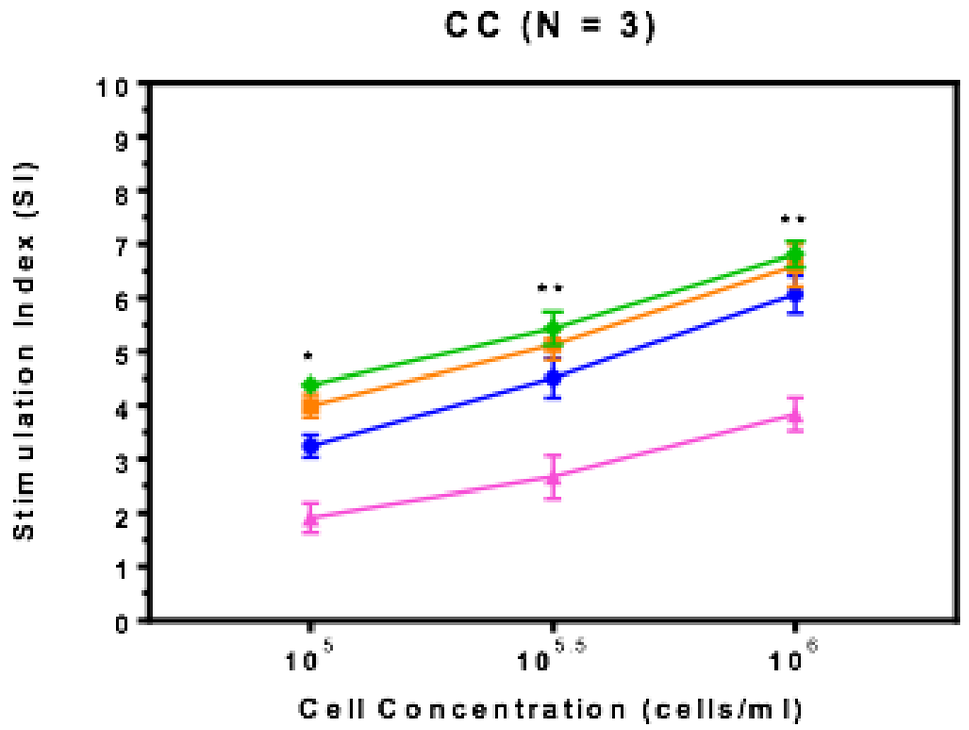
Aetiopathogenesis

STAPHYLOCOCCAL ANTIGENS PRODUCE STIMULATION OF LYMPHOCYTES FROM CAPSULAR CONTRACTURE BUT DO NOT STIMULATE BIA-ALCL TUMOUR CELLS





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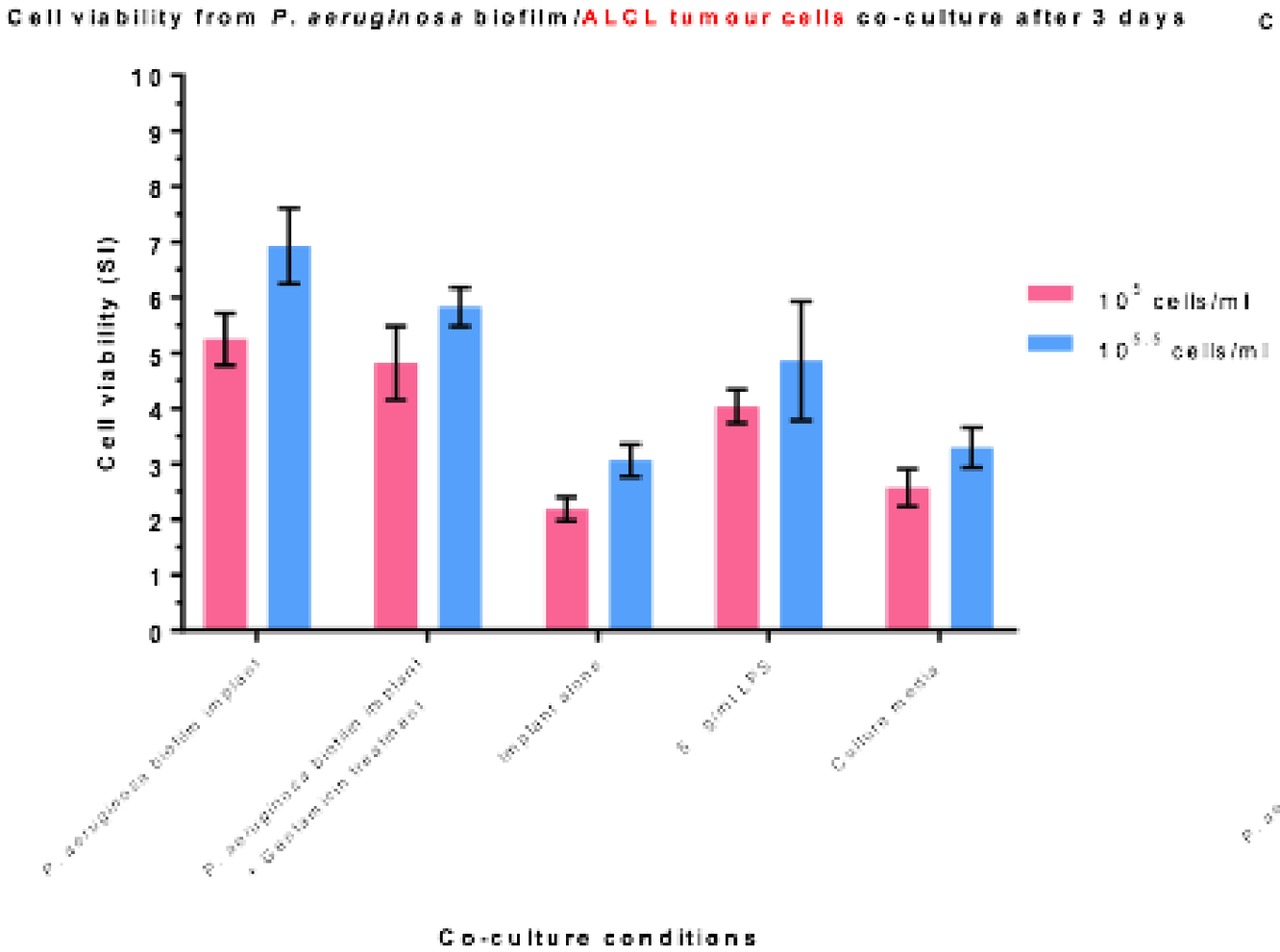
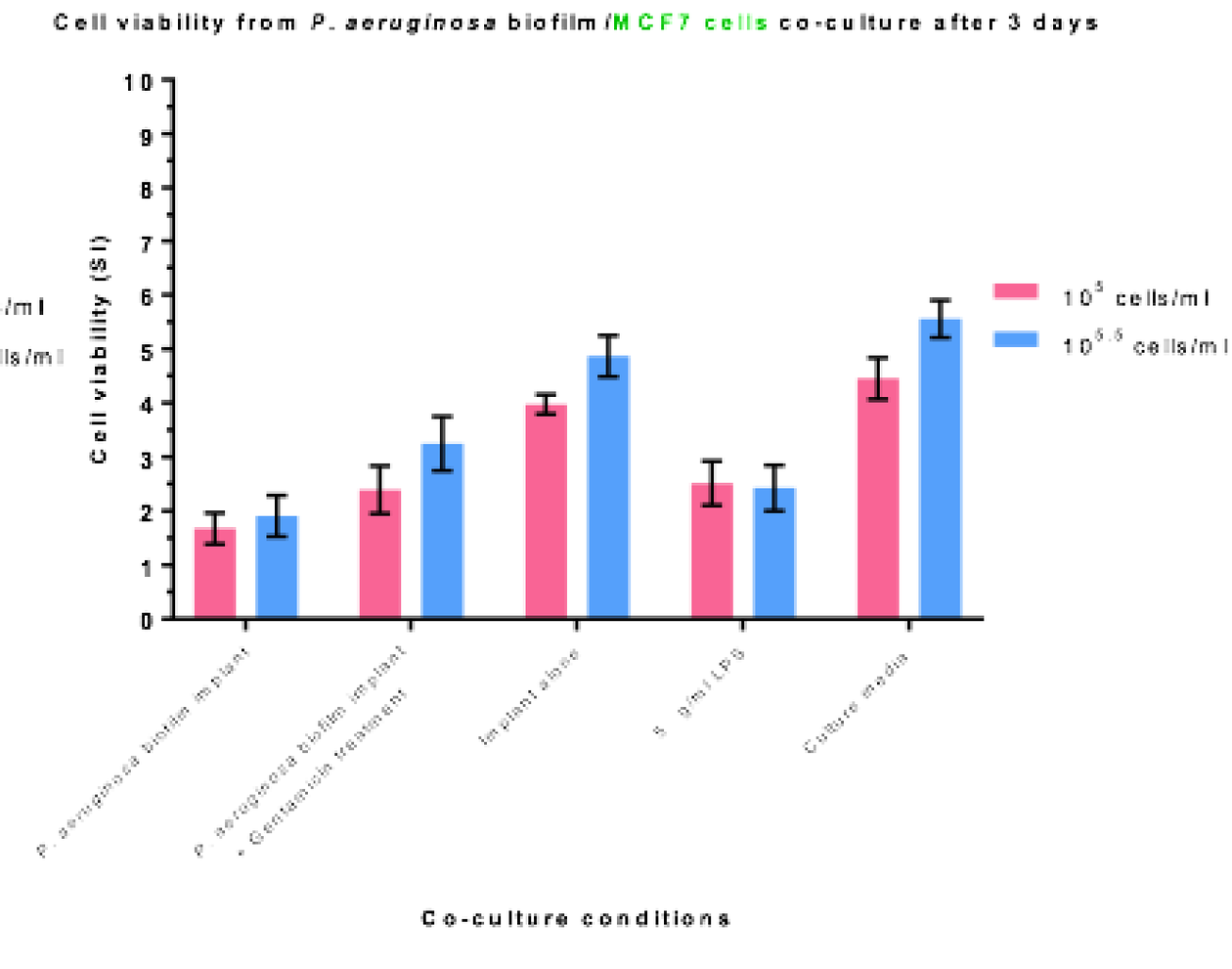
Aetiopathogenesis

IN CO CULTURE EXPERIMENTS - PRESENCE OF GRAM NEGATIVE BACTERIA/LPS PRODUCES SIGNIFICANT BIA-ALCL TUMOUR PROLIFERATION





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Aetiopathogenesis

GRAM NEGATIVE/LPS PRODUCES DIFFERENTIAL PROLIFERATION

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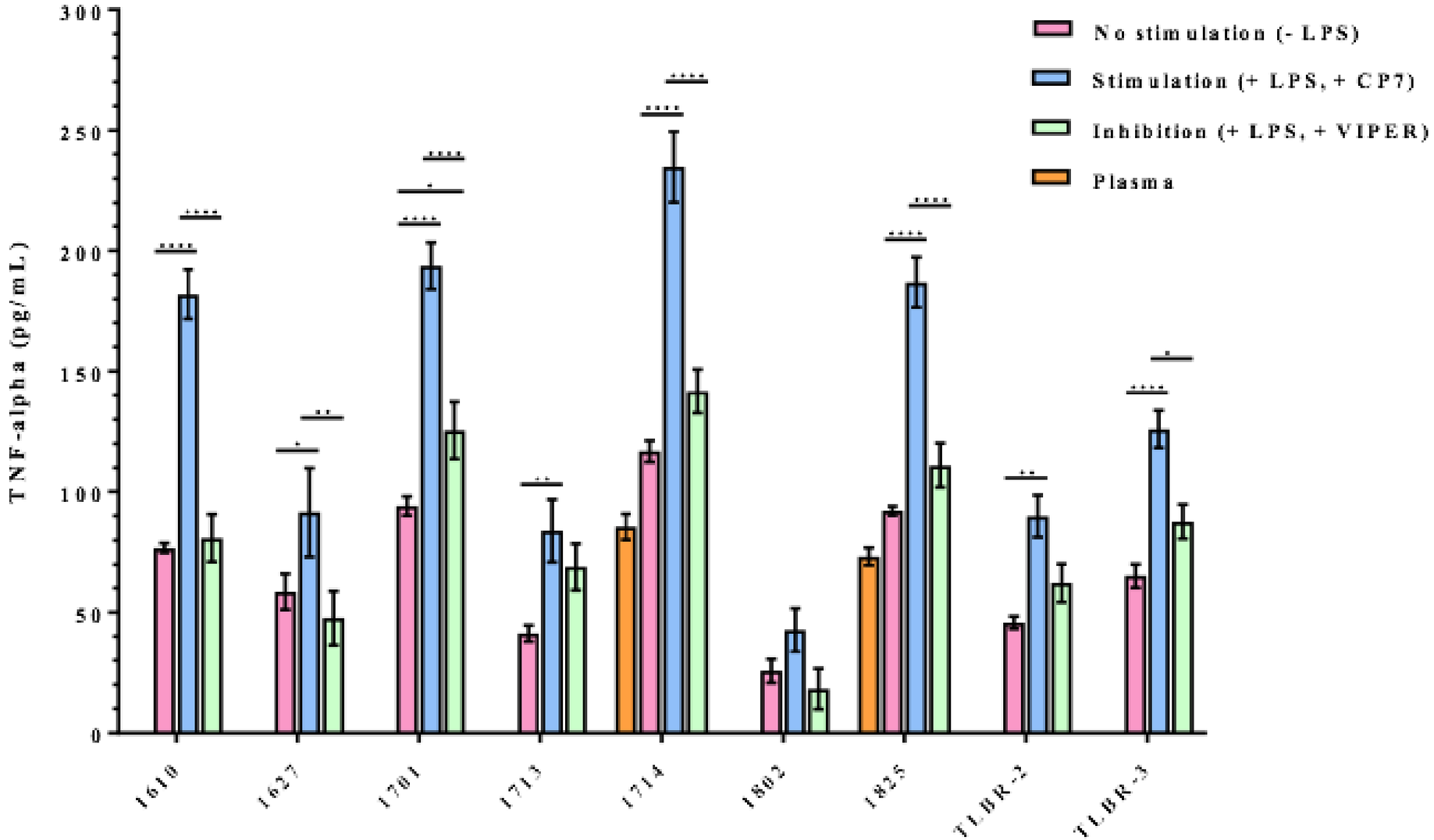
Aetiopathogenesis

TLR4 BLOCK DAMPENS LPS PROLIFERATION

TLR4 inhibitor peptide inhibits LPS-induced activation in BIA-ALCL tumour cells



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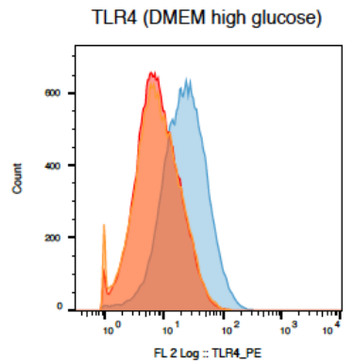
Aetiopathogenesis

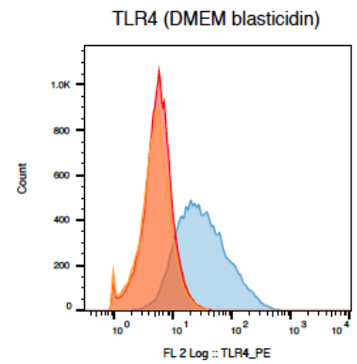
TLR4 NOW DEMONSTRATED IN CYTOPLASM OF BIAALCL TUMOUR CELL LINES

TLR4 (DMEM high glucose)

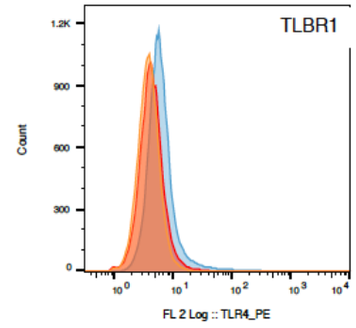


Sample Name	Count
#1 E071018 tlr4 DMEM hi glucose unstained + ZombieNIR control.fcs	33322
#2 E071018 TLR4 DMEM hi glucose + secondary MAb_PE + ZombieNIR control.fcs	33779
#3 E071018 TLR4 DMEM hi glucose + anti_TLR4_PE + ZombieNIR control.fcs	33245

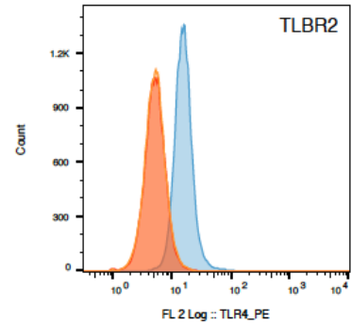
TLR4 (DMEM blasticidin)



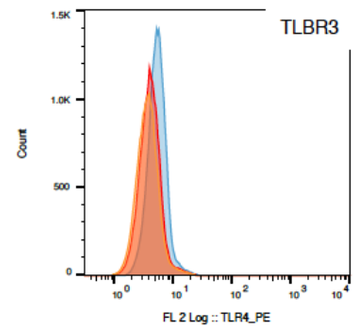
Sample Name	Count
#4 E071018 TLR4 DMEM blasticidin unstained + ZombieNIR control.fcs	28176
#5 E071018 TLR4 DMEM blasticidin + secondary MAb_PE + ZombieNIR control.fcs	31609
#6 E071018 TLR4 DMEM blasticidin + anti_TLR4_PE + ZombieNIR control.fcs	29625



Sample Name	Count
#7 E071018 TLBR1 unstained + ZombieNIR control.fcs	26075
#8 E071018 TLBR1 + secondary MAb_PE + ZombieNIR control.fcs	26223
#9 E071018 TLBR1 + anti_TLR4_PE + ZombieNIR control.fcs	28214



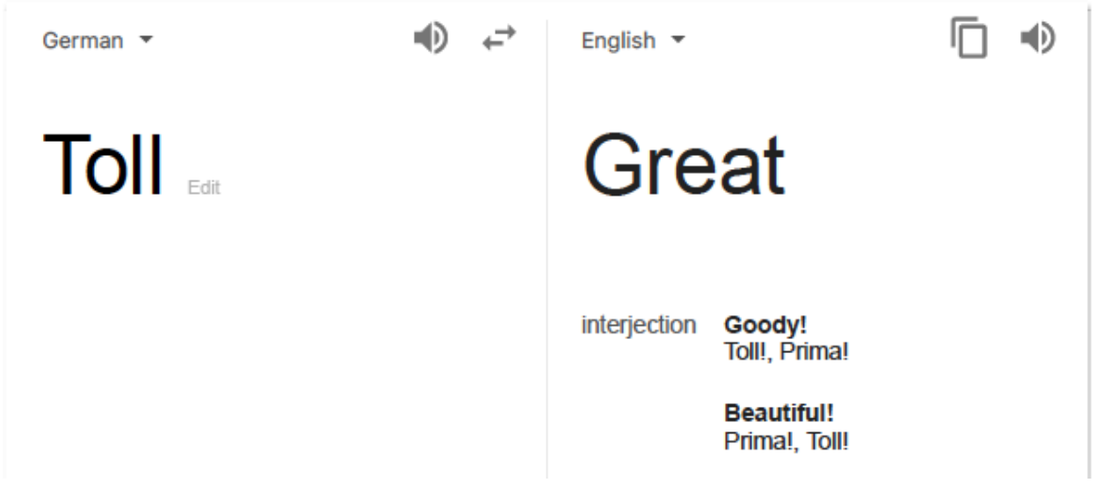
Sample Name	Count
#10 E071018 TLBR2 unstained + ZombieNIR control.fcs	27233
#11 E071018 TLBR2 + secondary MAb_PE + ZombieNIR control.fcs	26122
#12 E071018 TLBR2 + anti_TLR4_PE + ZombieNIR control.fcs	27489

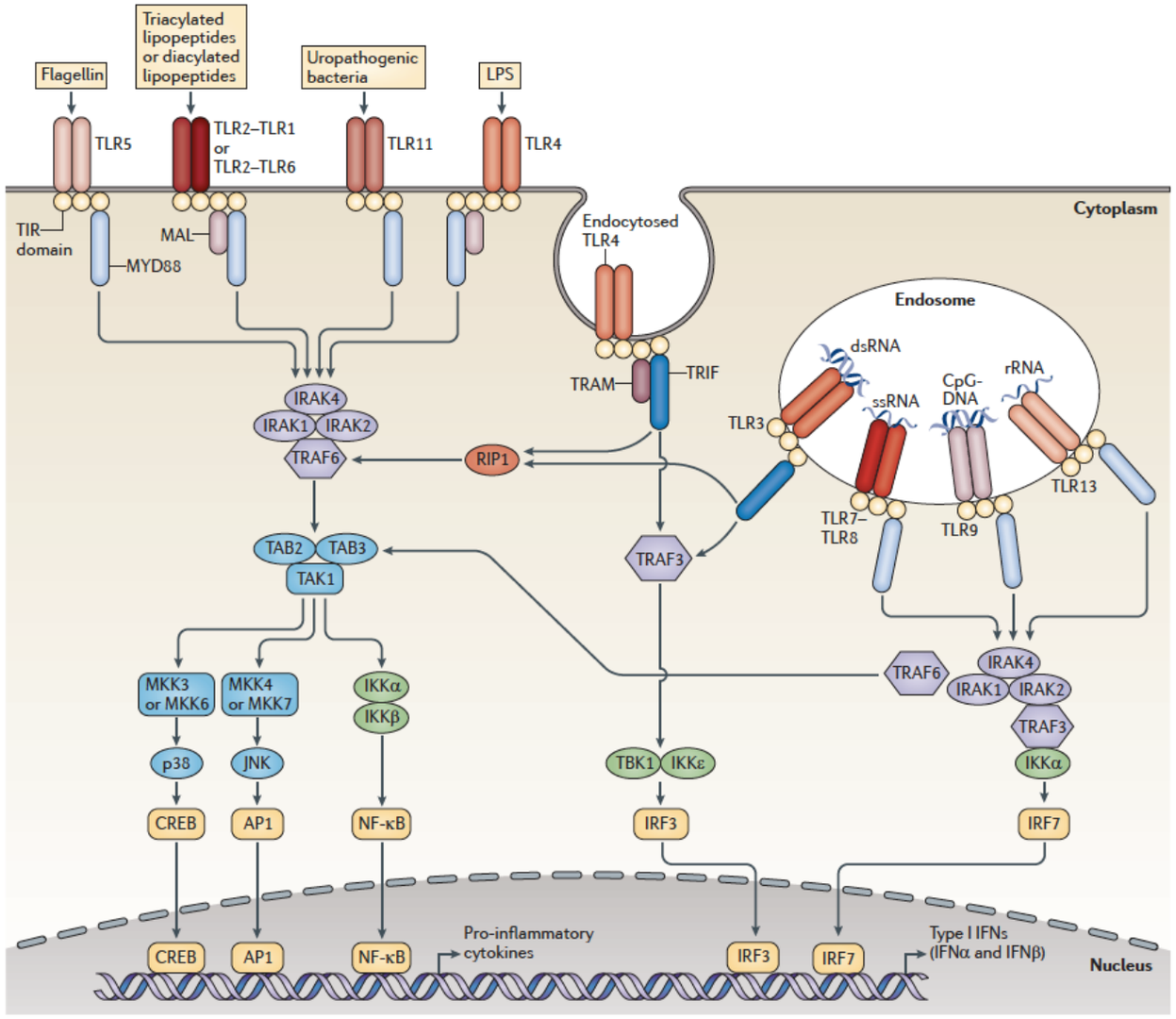


Sample Name	Count
#13 E071018 TLBR3 unstained + ZombieNIR control.fcs	25590
#14 E071018 TLBR3 + secondary MAb_PE + ZombieNIR control.fcs	26989
#15 E071018 TLBR3 + anti_TLR4_PE + ZombieNIR control.fcs	28863

Toll Like Receptors

- Important event for immunology with award of Nobel Prize in 2011 to Jules Hoffman and Bruce Beutler
- Central role in innate immunity and response to pathogens including LPS
- Driver of inflammation and release of inflammatory cytokines
- Potential for promotion of adaptive immune response and prevention of disease





Frequent activating STAT3 mutations and novel recurrent genomic abnormalities detected in breast implant-associated large cell lymphoma

Surgical Infection Research Group, Macquarie University
Peter MacCallum Cancer Cancer Center and Epworth Healthcare
Walter and Eliza Hall Institute of Medical Research
Prince of Wales Hospital, Princes Alexandra Hospital
Australia

[redacted]

Genetics

- 11 consecutive cases
- Aberrant JAK/STAT signalling found as a central pathogenic abnormality (vs normal population 1 in 10,000 or less)
- Found in systemic ALCL
- Also found novel deletion of RPL5 (ribosomal protein genes) common in melanoma/breast ca and amplifications of Receptor activator of nuclear factor (RANK) - implicated in progesterone mediated breast ca
- Relationship with TP53 oncogene already described (vs normal population 1 in 10-50,000 or less)

Strengthens unifying hypothesis

ID	Stage of Disease	Gene
BALCL1	T2N0M0	STAT3
		BCOR
BALCL2	T1N0M0	STAT3
BALCL3	T4N0M0	TP53*
BALCL4	T1N0M0	SOCS1
BALCL5	T1N0M0	STAT3
BALCL6	T2N0M0	TP53
		STAT3
		TP53*
		SETD2
BALCL7	T1N0M0	STAT3
BALCL8	T1N0M0	JAK1
		JAK3*
BALCL9	T1N0M0	STAT3
BALCL10	T1N0M0	STAT3
BALCL11	T1N0M0	PTPN1
		PRKCB

[redacted]

Aetiopathogenesis

INFLAMMATORY TRIGGER

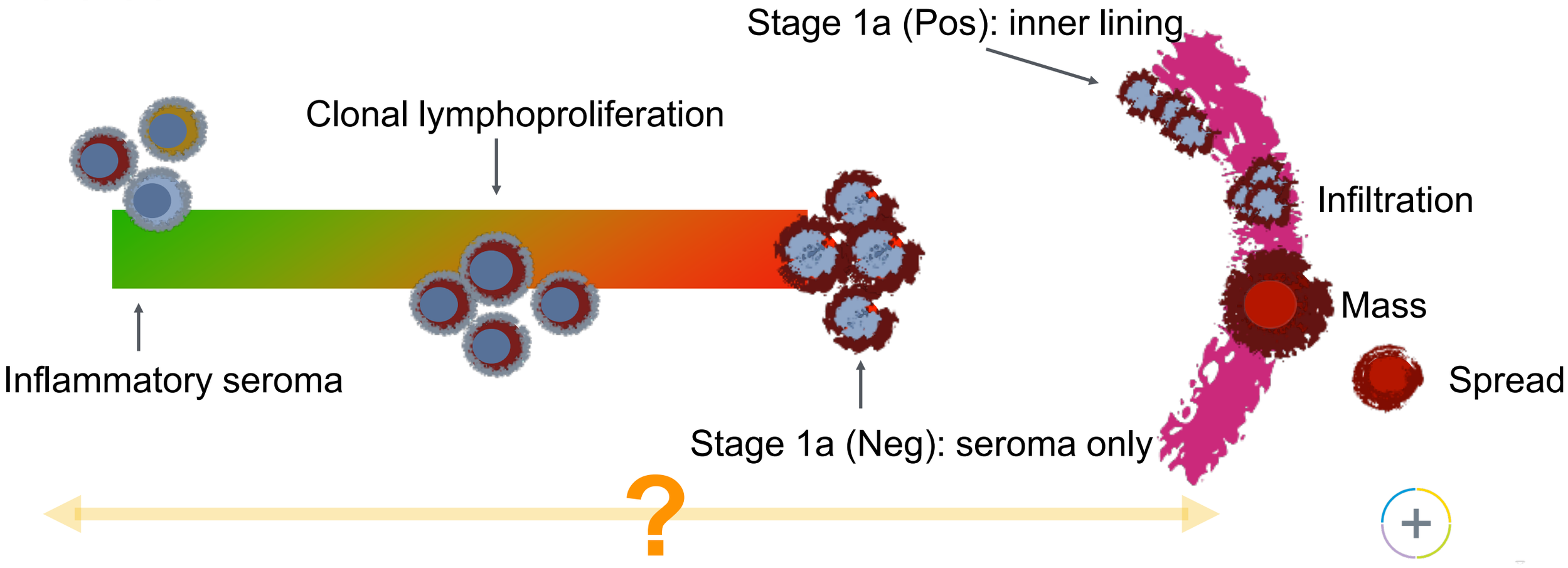
Trigger	Bacteria	Allergy	Friction	Particles
Cause inflammation	Yes	Yes	Yes - trauma	Maybe
Differential risk for textured implants	Yes	Maybe	Yes	Yes
Biological plausibility	Yes	Yes	Maybe	Maybe
Epidemiology - clusters	Yes	Maybe	No	No
Path to lymphomagenesis	Yes	Maybe	No	No
Backed by wider literature	Yes	No	No	No
Existing models of lymphomagenesis	Yes	No	No	No
Direct evidence of Antigenic stimulation	Yes	No	No	No

[redacted]

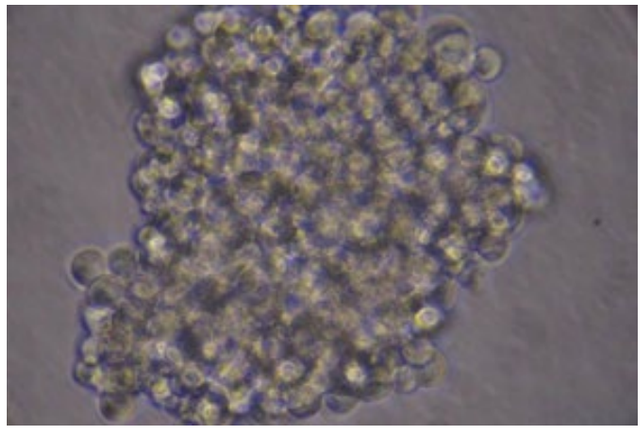
Stage 1a disease

STAGE 1A : INDOLENT, CURABLE - IS IT LPD?

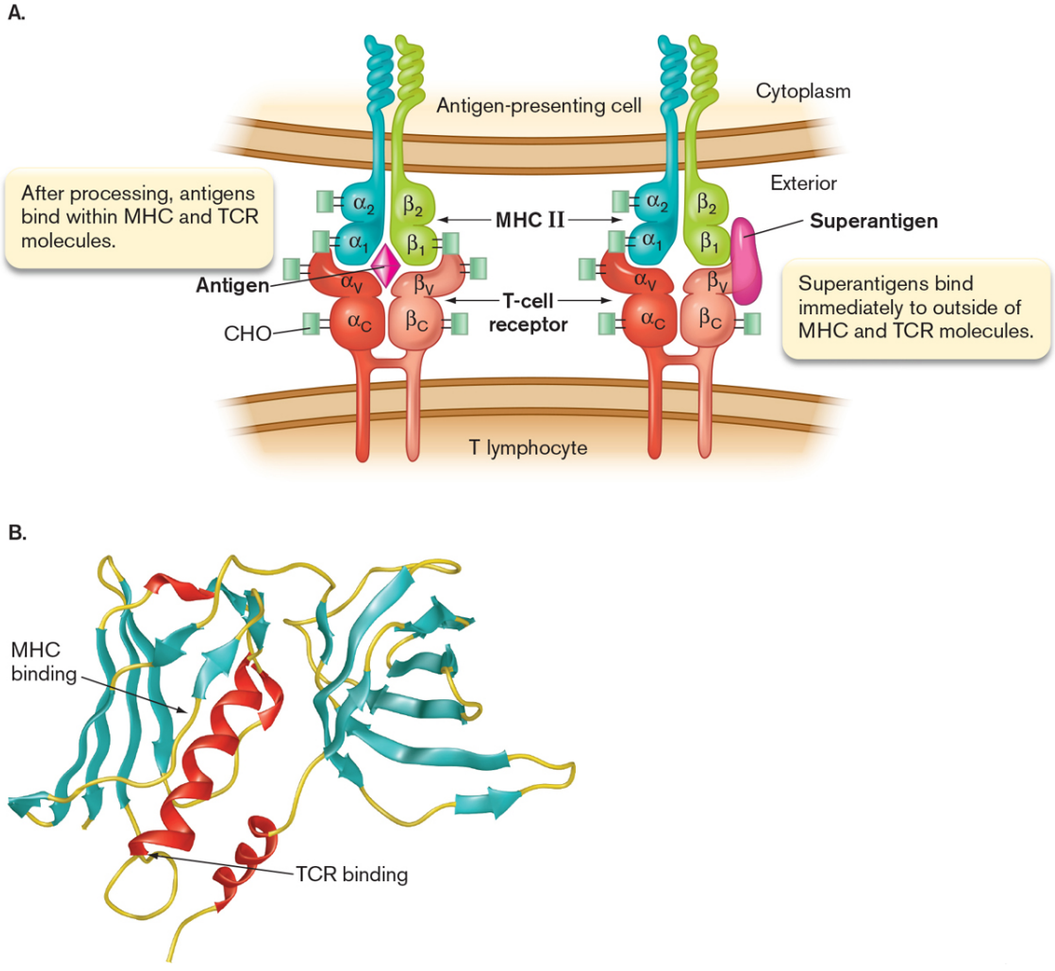
- Focus on Stage 1a disease which represents 78.9% of disease in ANZ
- Pattern is being replicated in other countries - except for US, under-reporting for cost/medicolegal reasons
- Is this spectrum with LPD or perhaps related to benign inflammatory seroma?
- At present, we are unable to distinguish which patients will remain indolent and which will progress to spread
- Further answers from study of genetics/bacteria and solid tumour presentations will give us answers



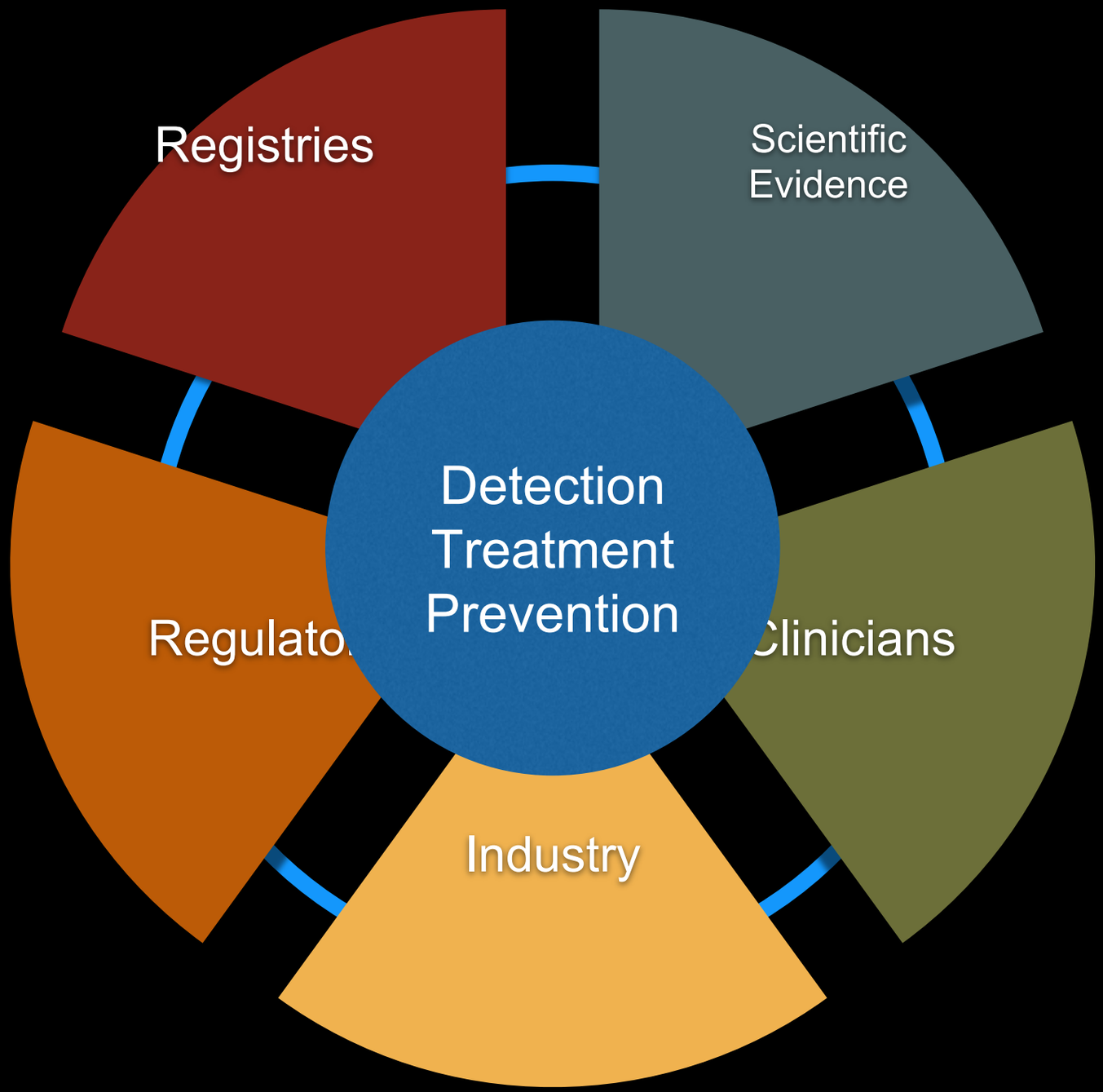
WORKS IN PROGRESS 2018



- Tumour cell stimulation assays - various antigens
- T cell transformation pathways
- Further study of microbiome in fresh BIA-ALCL samples and comparison with contracture, exchange
- Investigation of clusters
- What causes progression in stage 1A - genetics vs microbiome
- Reconstruction of BIA-ALCL smooth vs fat vs autologous
- HLA and genetic screening of patients



COLLABORATION, SCIENCE, FACTS AND TRUTH FREE FROM COI THROUGH TRANSPARENT DISCLOSURE RATHER THAN SPECULATION, OPINION AND FICTION



- Collaboration between researchers, clinicians, regulators, registries & industry builds trust/truth
- Evidence and research driving best practice = translational benefit to patients
- Transparent declaration of conflict(s)
- Motivation has to be pure - we want to solve ALCL, prevent it and thereby improve the standards and outcomes of breast implant surgery