Breakout Session II: Tumor Microenvironment (TME) Summary – Action Points

Panel: Steffi Oesterreich, Fatima Mechta-Grigoriou, Valerie Brunton, Julia Foldi, Marleen Kok

Patient Advocates: Pamela Robinson Kinnon, Tone Lien, Tracy Cushing

Chair: George Sflomos

Outline – TME

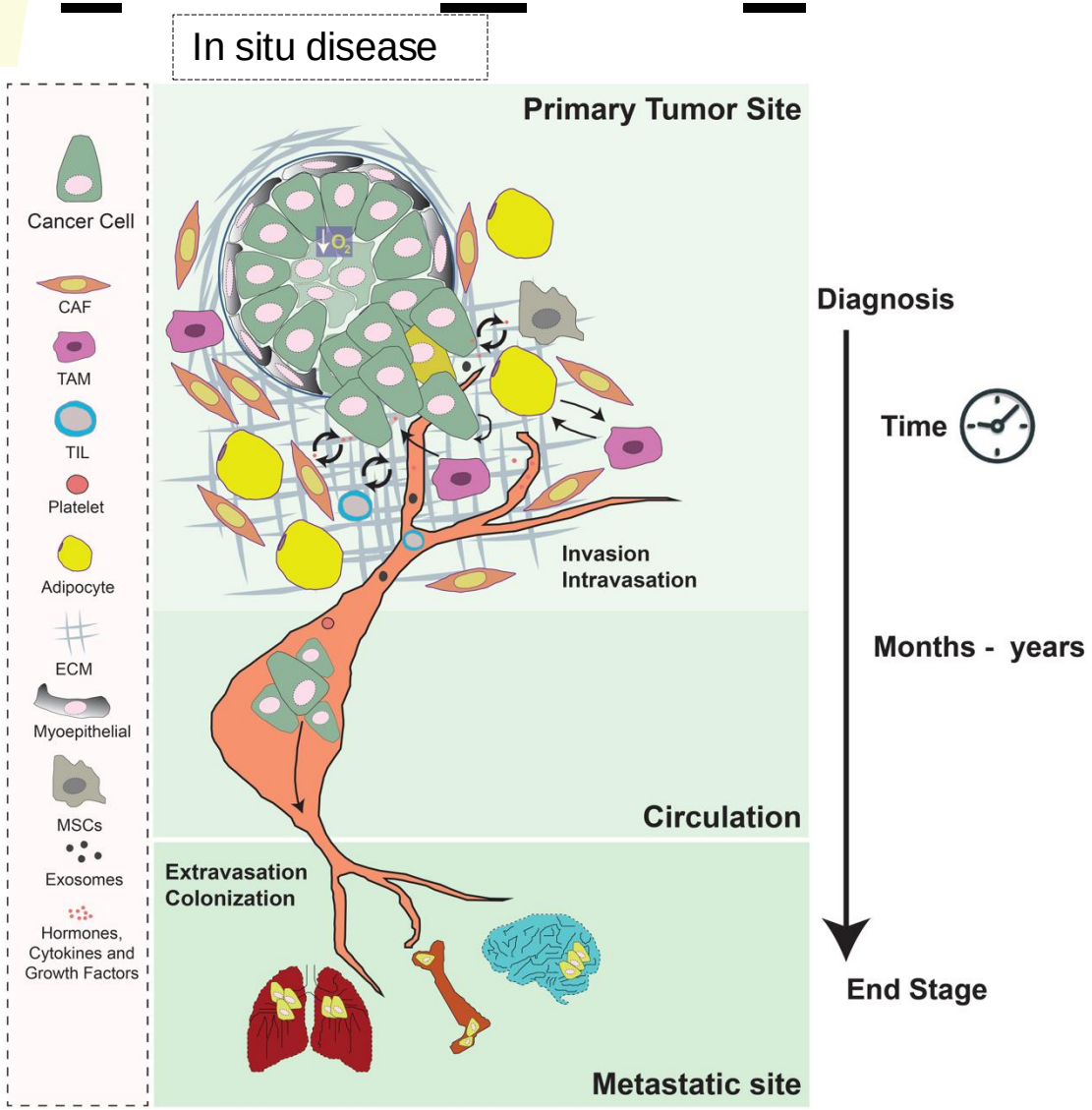
1. **ILC immuno-environment & Immunotherapies**, **Reproductive Factors**, **Lifestyle**, and **Aging TME** (Prof. Steffi Oesterreich)

2. **Role of Fibroblasts** in Immunosuppression & Resistance to Immunotherapies (Prof. Fatima Mechta-Grigoriou)

3. TME and **Preclinical Lobular Models** (Prof. Val Brunton)

4. Discussion/Perspectives (Tracy Cushing, Tone Lien, Pamela Kinnon) & Discussion

Tumor MicroEnvironment TME



Sflomos G and Brisken C., 2017 Breast Cancer (Springer)

→ Complex and Dynamic

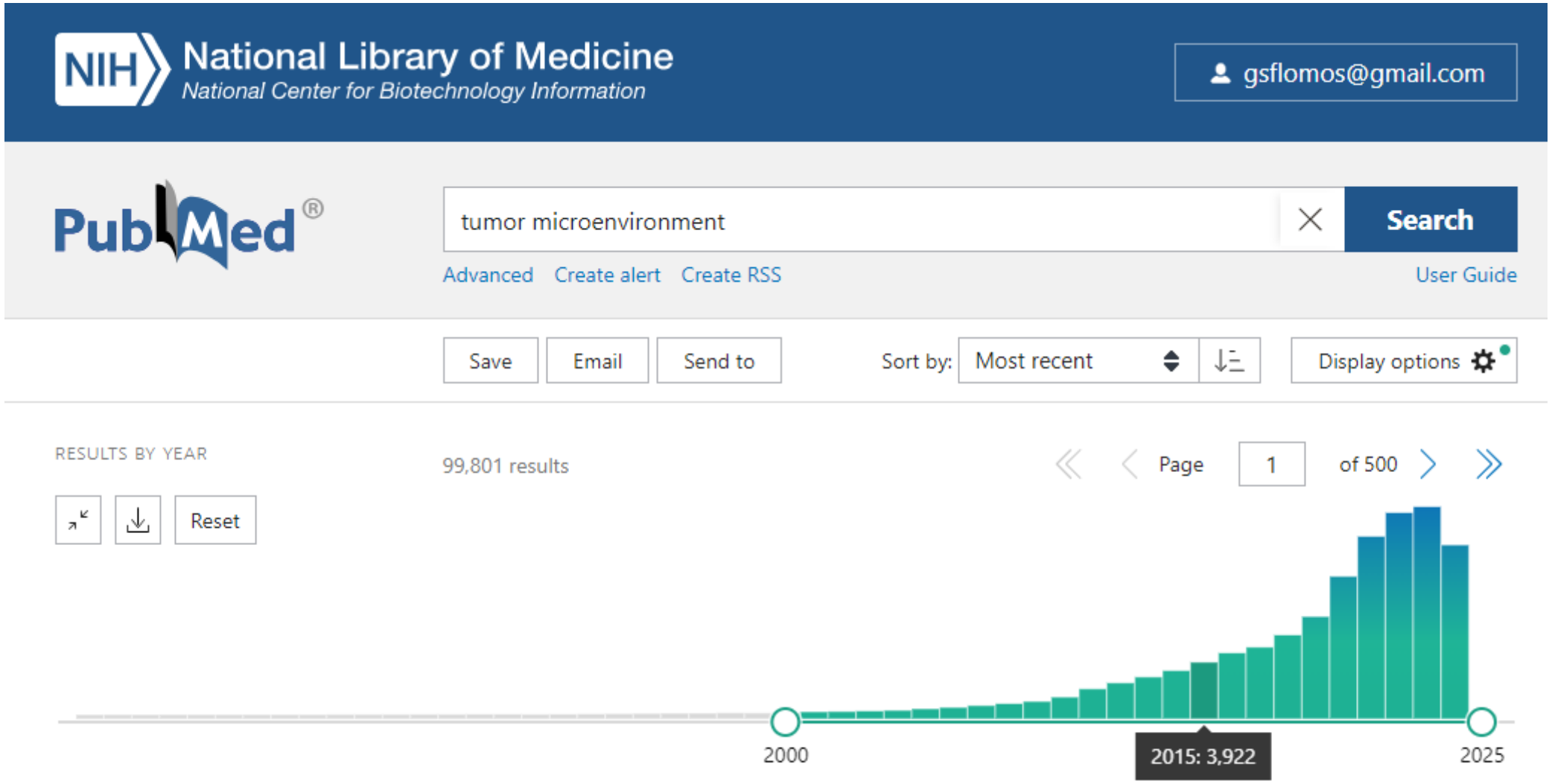
→ Heterogeneous

→ A plethora of (lobular) TMEs

- Intra-tumoral TME heterogeneity
- Inter-tumoral TME heterogeneity

→ Cellular (normal & cancer associated) & Acellular Components

Tumor MicroEnvironment (TME)



Understanding ILC immuno-environment

→**Lower overall immune infiltration** but a relatively **higher proportion of Macrophages** in ILC.

→**Increased TILs** in pleomorphic vs non-pleomorphic ILC cases.

Understanding ILC response to immuno-therapies

→Targeting immune cells **other than T cells** (CAFs, adipocytes).

→**ILC variants** when studying **immune infiltration** (and designing trials).

→Further characterization of **the role of macrophages** in the biology of ILC (pleomorphic).

Age and Inflamed TME in ILC

→ILC is diagnosed more commonly in older women than NST.

→Inflamed aged TME **causes immune dysfunction** in older breast cancers.

→**Increased Risk** with Late Age at First Full Term Birth and Nulliparity for ILC - Increased Lactogenic Gene Expression.

→**Limited clinical trials for patients with ILC.**

Different TME in ILC vs NST

→ Fibroblast-related Tumor micro-environment **is different** in lobular vs NST tumors.

→ILC is enriched in inflammatory **CAF (Detox-iCAF)** and not ECM-myCAF compared to IDC.

→Lack of E-cadherin **promotes accumulation of iCAFs** but **reduces cytotoxicity** of ITGAE/CD103+ TRM CD8+ T lymphocytes (classic ILC).

TME and Preclinical Lobular Models

→Patient-derived mouse models of ILC

→**immune deficient**

→Moving forward – in vitro/ex vivo approaches

→Organoid co-cultures

→Organ-on-chip

→Possible new TME-associated ECM targets in ILC

→**ECM remodeling enzyme (LOXL1)**

TME and Preclinical Lobular Models

ILC 2024 Leuven, Belgium

→Modelling ILC **interplay with adipocytes/CAFs**.

→Understand/Model ILC **response to immunotherapies**.

→Modelling **metastatic TME/outgrowth/dormancy**.

→ Implementation of clinical trials for ILC patients.

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