The Link Between the Immune Microenvironment and Outcome in Colorectal Cancer

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Disclosures

Co-founder and chairman of the scientific advisory board:
  - HalioDx

Collaborative Research Agreement (grants):
  - Perkin-Elmer, IObiotech, MedImmune, Janssen, Imcheck Therapeutics

Participation to Scientific Advisory Boards:
  - BMS, MedImmune, Astra Zeneca, Novartis, Definiens, Merck Serono, IObiotech, ImmunID, Nanostring, Illumina, Northwest Biotherapeutics, Actelion, Amgen, Merck MSD

Consultant:
  - BMS, Roche, GSK, Compugen, Mologen, Gilead, Sanofi
Cancer is one of the most complex biological system of all

“The whole is greater than the sum of its parts”, Aristotle

-> Systems biology in human cancer
What is the importance of the pre-existing immunity within tumors? Does it matter?

Cancer patient

Current cancer classification
Tumor cell characteristics
Tumor cell extension and invasion
Anatopathology
Tumor Morphology
Tumor cell of origin
Tumor Molecular pathway
Tumor Gene expression
Tumor Mutation status

Immune-based classification
Host immune response
Currently NONE

Grade
Budding
Etc...
Stem cell
Goblet cell
Etc...
MSI
CIN
Etc...
CMS
Etc...
P53
KRAS
BRAF
Etc...
A Novel Paradigm for Cancer

Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome

Jérôme Galon,1*† Anne Costes,1 Fatima Sanchez-Cabo,2 Amos Kirilovsky,3 Bernhard Mlecnik,2 Christine Lagorce-Pagès,1 Marie Tosolini,1 Matthieu Camus,1 Anne Berger,4 Philippe Wind,4 Franck Zinzindohoué,5 Patrick Bruneval,6 Paul-Henri Cugnenc,5 Zlatko Trajanoski,6 Wolf-Herman Fridman,1,7 Franck Pagès2,7†

29 SEPTEMBER 2006 VOL 313 SCIENCE www.sciencemag.org

- Gene expression profiling
- Qualitative immune signature

The foundation a new concept

- Immunohistochemistry (IHC)
- Digital Pathology
- Quantitative immune cell infiltration

Optimized Immunosign

Quality

Inflammation
Adaptive immunity
Immune suppression

Survival

Disease Free Survival

0 20 40 60 80 100 120 140 160 180
0 0.2 0.4 0.6 0.8 1

Survival (months)

Type/Density/Location

Galon J et al. Science 2006
Immunoscore: a novel paradigm for cancer

Coordinated adaptive immune reaction (Immunoscore) more than tumor invasion predicts clinical outcome

Galon et al. Science 2006
A Novel Paradigm for Cancer

Multivariate Cox Analysis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-stage</td>
<td>1.2</td>
<td>0.25</td>
</tr>
<tr>
<td>N-stage</td>
<td>1.4</td>
<td>0.15</td>
</tr>
<tr>
<td>Differentiation</td>
<td>1.1</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Immunoscore</strong></td>
<td>1.9</td>
<td>0.00001</td>
</tr>
</tbody>
</table>

“Immune Contexture”:

- Cells ->
  - Type
- Quantity ->
  - Density
- Spatial ->
  - Location
- Quality ->
  - Immune **functional** orientation -> Immunoscore
  - Immunosign

Cox Multivariate analysis including Immunoscore

<table>
<thead>
<tr>
<th>COX analysis for DPS</th>
<th>HR</th>
<th>Log Rank P-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor (T) stage</td>
<td>1.24</td>
<td>0.29</td>
</tr>
<tr>
<td>N Stage</td>
<td>1.31</td>
<td>0.17</td>
</tr>
<tr>
<td>Gender</td>
<td>1.47</td>
<td>0.18</td>
</tr>
<tr>
<td>Number of total Lymph nodes</td>
<td>1.13</td>
<td>0.68</td>
</tr>
<tr>
<td>Histological grade</td>
<td>0.69</td>
<td>0.29</td>
</tr>
<tr>
<td>Mucinous Colloid</td>
<td>1.29</td>
<td>0.47</td>
</tr>
<tr>
<td>Occlusion</td>
<td>1.03</td>
<td>0.94</td>
</tr>
<tr>
<td>Perforation</td>
<td>4.03</td>
<td>0.0084</td>
</tr>
<tr>
<td><strong>Immunoscore</strong></td>
<td>0.65</td>
<td><strong>0.0003</strong></td>
</tr>
</tbody>
</table>

**TNM Staging in Colorectal Cancer: T Is for T Cell and M Is for Memory**

Elizabeth K. Roussant and Mary L. Dale, Tumor Vaccine Group, Center for Translational Medicine in Women’s Health, University of Washington, Seattle, WA.

**Histopathologic-Based Prognostic Factors of Colorectal Cancers Are Associated With the State of the Local Immune Reaction**

Bernhard Mlecnik, Marie Tosolini, Amos Kirilovsky, Anne Berger, Gabriela Bindas, Tohao Meatchi, Patrick Brunsva, Ziadko Trofimov, Wolf-Herman Friedman, Franck Pagot, and Jereme Galon

“TNM staging: T is for T cell and M is for Memory”

Editorial: Broussard et al. JCO 2011

Multivariate Analysis

<table>
<thead>
<tr>
<th>Cox Analysis</th>
<th>DFS</th>
<th></th>
<th>OS</th>
<th></th>
<th>DSS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>P-value</td>
<td>HR</td>
<td>P-value</td>
<td>HR</td>
<td>P-value</td>
</tr>
<tr>
<td>AJCC/UICC-TNM</td>
<td>1.38</td>
<td>0.09 ns</td>
<td>1.18</td>
<td>0.29 ns</td>
<td>1.43</td>
<td>0.10 ns</td>
</tr>
<tr>
<td>Immunoscore</td>
<td>0.64</td>
<td>&lt;0.0001</td>
<td>0.71</td>
<td>&lt;0.0001</td>
<td>0.63</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Galon et al. Science 2006, Mlecnik et al. JCO 2011

✓ An immune classification of cancer
✓ The power of the pre-existing immunity
✓ The possibility to unleash the immune response with immunotherapy
Prognostic importance of the \textit{in situ} immune reaction in patients with early-stage (Stage I/II) colorectal cancer

Evaluation in the Center (CT) and the Invasive margin (IM) of the tumor
Cohort 1 = 411 patients, cohort 2 = 188 patients

\begin{align*}
\text{D} & \text{CD45RO}_{\text{CT/IM}} \quad \text{CD8}_{\text{CT/IM}} \\
\text{P} & \text{<0.0001} \quad \text{HR} \\
(4)-\text{Hi} & 42\% \quad 1 \\
(3)-\text{Hi} & 27\% \quad 2.9 \\
\text{all patients} & \\
(1-2)-\text{Hi} & 27\% \quad 10.2 \\
(0)-\text{Hi} & 4\% \quad 23.1
\end{align*}

\text{COX multivariate analysis}

\begin{tabular}{|l|c|c|}
\hline
\textbf{Parameter} & \textbf{HR} & \textbf{P value} \\
\hline
\text{T-stage} & 1.2 & 0.41 \\
\text{Perforation} & 5.5 & 0.003 \\
\text{Immune pattern} & 0.3 & <0.00001 \\
\hline
\end{tabular}

Understanding the evolution of the immune response with tumor progression using systems biology

- The Immune Landscape in human cancer
- Evolution of the tumor microenvironment with tumor progression?
- Immune escape mechanisms in human tumors?

-> Spatio-temporal dynamics of the immune response with tumor progression

Bindea G et al. *Immunity*, 2013
What are the mechanistic relationships between tumor genotype and Immunoscore?

Integrative Analyses of Colorectal Cancer Show Immunoscore Is a Stronger Predictor of Patient Survival Than Microsatellite Instability

Bernhard Mlecnik,1,2,3,19 Gabriela Bindea,1,2,3,19 Helen K. Angell,1,2,3,4 Pauline Maby,1,2,3,5 Mihaela Angelova,1,2,3,6 David Tougeron,5,7,6 Sarah E. Church,1,2,3 Lucie Lafontaine,1,2,3 Maria Fischer,6 Tessa Fredriksen,1,2,3 Maristella Sass0,1,2,3 Amélie M. Billocq,1,2,3 Amos Kirilovsky,1,2,3 Anna C. Obenauf,9 Mohamad Hamieh,5 Anne Berger,1,10 Patrick Bruneval,11 Jean-Jacques Tuech,12 Jean-Christophe Sabourin,13 Florence Le Pessot,13 Jacques Mauillon,13,14 Arash Rafii,15 Pierre Laurent-Puig,7,16 Michael R. Speicher,9 Zlatko Trajanoski,9 Pierre Michel,7 Richard Sesboüe,5 Thierry Frebourg,5,16 Franck Pages,1,2,3,17 Viia Valge-Archer,4,18 Jean-Baptiste Latouche,5,8 and Jérôme Galon1,2,3,*

TCGA CRC cohort: n= 270 patients

Inserm cohort: n= 689 patients

Mlecnik et al. Immunity 2016
Mechanistic impact of DNA-mismatch repair deficiency

Increased frequency of Frameshift mutations

Genetic evidence of Immunoediting

Increased frequency of High-Immunoscore

Increased Proliferating T-cells, Th1, cytotoxic T-cells

Anti-TGFBR2mutFS Specific T-cells

Mlecnik et al. Immunity 2016

Anti-tumor T-cell killing
Immunoscore high (I3, I4) patients have prolonged survival regardless of the MSI status.
## Colorectal cancer classifications

<table>
<thead>
<tr>
<th>Ways to classify</th>
<th>T-STAGE</th>
<th>N-STAGE</th>
<th>M-STAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor cell extension and invasion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphology</td>
<td>Cell of origin</td>
<td>Molecular pathway</td>
<td>Mutation status</td>
</tr>
<tr>
<td>Mucinous</td>
<td>Enterocyte</td>
<td>CIN</td>
<td>BRAF</td>
</tr>
<tr>
<td>Medullary</td>
<td>Goblet-like</td>
<td>MSI</td>
<td>APC</td>
</tr>
<tr>
<td>Adeno. NOS</td>
<td>Transit-amplifying-R</td>
<td>CIMP</td>
<td>KRAS</td>
</tr>
<tr>
<td>Serrated</td>
<td>Transit-amplifying-S</td>
<td></td>
<td>TP53</td>
</tr>
<tr>
<td>Signet ring cell</td>
<td>Inflammatory</td>
<td></td>
<td>CTNNB1</td>
</tr>
<tr>
<td>Micropapillary</td>
<td>Stem-like</td>
<td></td>
<td></td>
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<tr>
<td>Cribriform comedotype</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Host immune response</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoscore</td>
<td>CD3+ T cells</td>
<td>CD8+ T cells</td>
<td>Density</td>
<td>Location (CT, IM)</td>
</tr>
</tbody>
</table>

Galon et al. *J Pathol.* 2014
The Immunoscore as a New Possible Approach for the Classification of Cancer

World Immunotherapy Council inaugural meeting (Feb 2012)

Support (moral) from the World Immunotherapy Council (WIC), and support from societies including, EATI, BDA, CCIC, CIC, CRI, CIMT, CSCO, TIBT, DTIWP, ESCII, NIBIT, JACI, NCV-network, PIVAC, ATTACK, TVACT...

Worldwide Immunoscore consortium (PI: J Galon)
(17 countries: >3000 Stage I/II/III Colon cancer patients)

Assay harmonization

Immunoscore meetings:
- Feb 2012, Italy
- Dec 2012, Italy
- Nov 2013, SITC, USA
- Dec 2013, Italy
- Jan 2014, Qatar
- Jul 2014, Paris, France
- Nov 2014, SITC, USA
- Nov 2015, SITC, USA
- Dec 2015, Italy
- Feb 2016, USCAP, USA
- April 2016, USA
- Nov 2016, SITC, USA
- Dec 2016, Italy
- Feb 2017, USCAP, USA
- Dec 2017, Italy
International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study

Relative variable contribution to risk

Chi squared proportion ($\chi^2$) test for clinical parameters

All patients

<table>
<thead>
<tr>
<th>Immunoscore</th>
<th>P-values</th>
<th>c-index</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 groups</td>
<td>&lt;0.0001</td>
<td>0.73 (0.66-0.80)</td>
</tr>
<tr>
<td>3 groups</td>
<td>&lt;0.0001</td>
<td>0.73 (0.67-0.80)</td>
</tr>
<tr>
<td>5 groups</td>
<td>&lt;0.0001</td>
<td>0.73 (0.67-0.80)</td>
</tr>
</tbody>
</table>

Cox Multivariate

*Pages et al. The Lancet 2018*
Immunoscore in locally advanced colon cancer

Stage III
Immunoscore in locally advanced colon cancer

Stage III

**Immunoscore prognostic value:**

- HEGP, Paris France cohort
- SITC, worldwide study
- N0147 phase 3 clinical trial
- IDEA, France, phase 3 clinical trial

- Predefined cut-off from Worldwide SITC study, and Predefined statistical plan (Mayo Clinic)
- 4 independent cohorts, 2514 patients
Phase 3 randomized study of stage III colon cancer patients (IDEA) 3 vs 6 months of chemotherapy (n=1062)

HR = 1.54 (95CI% 1.24-1.93), $P < 0.0001$

HR = 2.42 (95CI% 1.47-3.99), $P < 0.0001$

Demonstration of the **Prognostic** value of Immunoscore in a randomized cohort of Stage III colon cancer patients

ASCO 2019
Immunoscore in stage III colon carcinoma patients

✓ Predefined cut-off from Worldwide SITC study, and Predefined statistical plan (Mayo Clinic)
✓ 4 independent cohorts, 2514 patients

- N=147 (HEGP, France)
- N=763 (SITC, World)
- N=542 (N0147, USA)
- N=1062 (IDEA, France)

Immunoscore predicts High-risk and No-risk patients in stage III colon cancer
Immunoscore in locally advanced colon cancer

Stage III

Immunoscore Predictive value:

✓ IDEA, France, phase 3 clinical trial (3 months vs 6 months chemotherapy)
Phase 3 randomized study of stage III colon cancer patients (IDEA) 3 vs 6 months of chemotherapy (n=1062)

All Stage III treated with FOLFOX

High Immunoscore significantly **predicts** response to 6 months FOLFOX chemotherapy in all Stage III patients

**ASCO 2019**
Phase 3 randomized study of stage III colon cancer patients (IDEA) 3 vs 6 months of chemotherapy (n=1062)

Low-Risk (T1-3 and N1)

High Immunoscore predicts response to 6 months FOLFOX chemotherapy in Low-Risk Stage III patients

High Immunoscore
- 6 months
- 3 months

HR=0.47 (95CI% 0.26-0.83), \(P=0.01\)

Low Immunoscore
- 6 months
- 3 months

HR=0.86 (95CI% 0.52-1.42), \(P=0.56\)

ASCO 2019
Phase 3 randomized study of stage III colon cancer patients (IDEA) 3 vs 6 months of chemotherapy (n=1062)

High-Risk (T4 or N2)

High Immunoscore

Low Immunoscore

High Immunoscore significantly predicts response to 6 months FOLFOX chemotherapy in High-Risk Stage III patients

HR=0.54 (95CI% 0.35-0.84), \( P=0.006 \)

HR=0.76 (95CI% 0.51-1.15), \( P=0.20 \)

ASCO 2019
International consensus Immunoscore SITC study: Stage III colon cancer patients treated or not treated with chemotherapy

High Immunoscore significantly predicts response to chemotherapy in Stage III patients

High Immunoscore

Low Immunoscore (I0)

High Immunoscore: P < 0.001

Low Immunoscore: P = 0.83
Conclusions: Stage III colon cancer patients

Immunoscore is a significant **prognostic** marker of survival in Stage III patients (Science 2006, J Clin Oncol 2011)

Immunoscore is a significant **prognostic** consensus marker of survival in Stage III patients (Lancet 2018, N0147 study, IDEA study)

**High** Immunoscore is significantly **predictive** of response to chemotherapy in Stage III colon cancer patients (SITC study)

**High** Immunoscore is significantly **predictive** of response to 6 months FOLFOX chemotherapy in Stage III colon cancer patients (IDEA study)

**Low** Immunoscore patients **do not respond** to chemotherapy (SITC study) nor to 6 months FOLFOX chemotherapy in Stage III colon cancer patients (IDEA study)
Is there an immune escape at the metastatic stage?

Stage IV
Metastasis analysis

One primary tumor

Colorectal cancer

Multiple metastatic sites

Liver Metastasis

Lung Metastasis

N=603 metastases

➢ Immunoscore within multiple metastases at different sites

Mlecnik et al. *JNCI* 2018
Van den Eynde M. et al. *Cancer Cell* 2018
Metastasis analysis

➢ Immunoscore within multiple metastases at different sites

Van den Eynde et al. Cancer Cell 2018
What drives metastasis?

What are the metastatic escape mechanisms?

A Novel theory of cancer evolution?
Current theories of cancer evolution

Models

- LINEAR
- NEUTRAL
- BIG-BANG
- BRANCHED

Immune pressure from Darwinian selection

- NO
- NO
- NO
- NO

- The 4 proposed theories of cancer evolution
- All theories are tumor cell-centric. None involves a role of the immune system.
Evolution of Metastases in Space and Time under Immune Selection

Mihaela Angelova,1 Bernhard Mlecnik,1,2 Angela Vasaturo,1 Gabriela Bindea,1 Tessa Fredriksen,1 Lucie Lafontaine,1 Bénédicte Buttard,1 Erwan Morgand,1 Daniela Bruni,1 Anne Jouret-Mourin,3 Catherine Hubert,3 Alex Kartheuser,3 Yves Humblet,3 Michele Ceccarelli,4,5 Najeeb Syed,6 Francesco M. Marincola,7,8 Davide Bedognetti,8,10 Marc Van den Eynde,1,3,10 and Jérôme Galon1,11,*
What drives metastasis?

- Primary tumors
- Synchronous metastases
- Metachronous metastases
- Metachronous metastases
- Metachronous metastases

Multi-Omics technologies

- Primary colorectal cancer
- Lung metastases
- Liver metastases
- Peritoneal metastases

Chromosomal Instability
- Mutations
- Tumor Genetics
- Tumor-gene expression

Vessels
- Host Immune
  - Microenvironment
- Immune Cells

> 11 years
Genomics of primary tumors and metastases

- Highly heterogeneous genomic patterns between metastases
Clonal dissemination – Parent/child-relationship

Primary tumors

Synchronous meta

Metachronous meta

11 years
Clonal evolution and cancer evolvogram

Non-recurrent clones are immunoedited. Progressing clones are immune privileged.
Immunomics patterns and immune cell infiltration within metastases

Angelova M. et al. *Cell* 2018
Cox multivariate analysis revealed 4 parameters associated with metastatic dissemination:

- Immunoscore
- Immunoediting
- The distance between CD3 T-cells and Ki67+ tumor cells
- The size of the parent metastasis

### Multivariate analysis of all genomics and immunomics parameters

<table>
<thead>
<tr>
<th>Excluded variable</th>
<th>Df</th>
<th>First recurrence</th>
<th>Multiple recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;none&gt;</td>
<td>43.3</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>CD3 to CK+Ki67+ mutual neighbor distance (Hi)</td>
<td>1</td>
<td>43.7</td>
<td>-2.2</td>
</tr>
<tr>
<td>Immunoscore (&gt;60%)</td>
<td>1</td>
<td>46.2</td>
<td>-3.1</td>
</tr>
<tr>
<td>Immunoediting (Low)</td>
<td>1</td>
<td>48.1</td>
<td>-3.1</td>
</tr>
<tr>
<td>Meta Size (log)</td>
<td>1</td>
<td>45.9</td>
<td>2.5</td>
</tr>
</tbody>
</table>

The table above shows the AIC log(HR) values for first and multiple recurrences, with the CD3 to CK+Ki67+ distance (Hi) and other parameters highlighted. The star denotes the significant parameters.
Validation Study

CRC Primary tumor recurrence (n=132 patients)

Immunoediting

Predictive model

Immunoediting and Predictive model are predictive factors of recurrence.
What drives metastasis? Conclusions

Different escape mechanisms delineated by lack of adaptive immunity or immunoediting.

Angelova M. et al. Cell 2018
What drives metastasis? Conclusions (2)

- Multiverse of metastases evolution in space and time under immune selection
- Evolution of tumor clones is linked to the intra-metastatic immune contexture.
- Non-recurrent clones are immunoedited. Progressing clones are immune privileged.

Angelova M. et al. Cell 2018
Parallel selection model describes tumor evolution during the metastatic process. Immunoediting and Immunoscore are predictive factors of metastasis recurrence. Distance between CD3+ cells and tumor cells Ki67+ and metastasis size are also associated with metastasis recurrence.

Angelova M. et al. *Cell* 2018
A Novel theory of cancer evolution

Models

LINEAR  NEUTRAL  BIG-BANG  BRANCHED  SELECTION

Immune pressure from Darwinian selection

NO  NO  NO  NO  YES

➢ Parallel immune selection model
➢ Dynamic interaction of tumor-cells with immune-cells and Darwinian selection of immune escape variant, with parallel evolution and multiverse of metastases.
Metastatic colorectal cancer patients: For clinical routine

Stage IV

**Pathological score**
- Steatohepatitis, HGP, NRH, TRG, R status, Number of lesions,

**Molecular status**
- RAS mutations

**Immunoscore**
- Consensus Immunoscore applied to metastases
Metastatic colorectal cancer patients: For clinical routine

Chi squared proportion ($\chi^2$) test for clinical parameters: Relative contribution to the risk test

Among molecular status, pathological parameters and Immunoscore, only Immunoscore has a significant contribution to the risk of TTR and OS

Immunoscore has the highest contribution to the risk of death in metastatic disease
Deciphering the tumor immune microenvironment:
Clinical implications

“Cold” Tumor
I 0

“Hot” Tumor
I 4

Clinical implications

Predictions
Need T-cell priming
Cancer vaccine

Response to immunotherapies
(CTLA4, PD1, PDL1, …)

But it is not as simple since biology is complex and is not dichotomized in good & bad
Treating hot, altered and cold immune tumors with immunotherapy

Galon J. & Bruni D.
Nature Reviews Drug Discovery 2019
Approaches to treat immune hot, altered and cold tumours with combination immunotherapies

Jérôme Galon* and Daniela Bruni

Absent
Low Immunoscore
Cold
Non-inflamed

Altered
Intermediate Immunoscore
Excluded
CT-Lo, Hi-IM

Optimal
High Immunoscore
Hot
Inflamed

Response to T cell checkpoint inhibition
Stratification of cancer based on the immune status

<table>
<thead>
<tr>
<th>Tumor classification</th>
<th>Molecular Mutations</th>
<th>MSI-H A</th>
<th>MSS^ B</th>
<th>MSS/CIMP.hi C</th>
<th>MSS D</th>
<th>MSS-CIMP.lo E</th>
</tr>
</thead>
</table>

**Immune classification**

-> Importance of having standardized immune Assays
Galon lab.
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   Bénédicte Buttard
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   Adrian Bot, John Rossi

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Research Branch, Sidra Medical and Research Centre, Doha, Qatar
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