Gene fusions in cutaneous melanocytic tumours

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Biopathology lab
Cancer care center Leon Berard
Lyon, France
Financial disclosures: none
Professional background

• Fully trained in clinical dermatology
• Fully trained in surgical pathology
• PhD oriented toward cytogenetic studies of skin lymphomas
Current position

- Senior pathologist in a cancer care hospital
- >90% worktime reviewing melanocytic consultation cases (>2000/year)
Capsule summary
How to discover new genetic alterations?

• Pathological review of unclassified cases
• Whole-exome RNA-sequencing
• Integrative analysis
How to discover new genetic alterations?

State of mind

Pan-genomic tools          Samples
Voyage in the grey zone

True       Possible/Plausible       False
« Out of the box » thinking

Dogmatism  
Research  
Progress
Making sense of big and small data
Layout of talk

• Current classification scheme of melanocytic tumours
• Focused «small data» research approach to find new anomalies
• 3 examples
WHO 2018: 9 classes of melanocytic tumours

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Low UV radiation exposure/CSD</th>
<th>High UV radiation exposure/CS</th>
<th>Malignant neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endpoint of pathway</td>
<td>Low-CSD melanoma/SSM</td>
<td>High-CSD melanoma/IMM</td>
<td>Desmoplastic melanoma</td>
</tr>
<tr>
<td>Benign neoplasms (naevi)</td>
<td>Naevus</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Intermediate / low-grade dysplasias and melanocytes</td>
<td>Low-grade dysplasia</td>
<td>BAP1-inactivated melanocytoma/MELTUMP</td>
<td>Lentigo maligna (MIS)</td>
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<tr>
<td>Intermediate / high-grade dysplasias and melanocytes</td>
<td>High-grade dysplasia/MIS</td>
<td>Deep penetrating melanocytoma/MELTUMP</td>
<td>Lentigo maligna (MIS)</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>Low-CSD melanoma/SSM (VGF)</td>
<td>Melanoma in BIN (rare)</td>
<td>LMM (VGF)</td>
</tr>
<tr>
<td>Common mutations</td>
<td>BRAF p.V600E; NRAS</td>
<td>BRAF or NRAS + BAP1</td>
<td>NRAS; BRAF (non-p.V600E)</td>
</tr>
</tbody>
</table>

**Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes**

BIN, BAP1-inactivated naevus; BN, blue naevus; CBN, cellular blue naevus; CN, congenital naevus; CSD, cumulative sun damage; DPN, deep penetrating naevus; IAMP, intraepidermal atypical melanocytic proliferation; IAMPUS, intraepidermal atypical melanocytic proliferation of uncertain significance; IMM, intraepidermal melanocytic proliferation without dysplasia; LMM, lentigo maligna melanoma; low-high-CSD, melanoma, melanoma in skin with a low-high degree of cumulative sun damage; MELTUMP, melanocytic tumour of uncertain malignant potential; MIS, melanoma in situ; PEM, pigmented spindle cell melanocytoma; SSM, superficial spreading melanoma; STUMP, spitzoid tumour of uncertain malignant potential; UV, ultraviolet; VGF, vertical growth phase (tumorigenic and/or mitogenic melanoma).
WHO 2018: 9 classes of melanocytic tumours

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Malignant Spitz tumour/ Spitz melanoma (lumorgenic)

<table>
<thead>
<tr>
<th>HRAS, ALK, ROS1, RET, NTRK1, NTRK3, BRAF, MET</th>
<th>CDKN2A</th>
</tr>
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CDKN2A; CCND2; CCND1; GAB2

Definitions: Melanocytoma is a tumorigenic neoplasm of melanocytes that generally has increased cellularity and/or atypia compared with a common nevus; tumorigenic means forming a mass of neoplastic cells.

Common mutations in each pathway are listed. Mutations already identified in benign or borderline low lesions are shown in bold.

Multi-dimensional classification
Multi-dimensional classification

- Sun exposure

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Multi-dimensional classification

- Sun exposure
- Topography

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### Definitions

A melanocytoma is a tumorigenic neoplasm of melanocytes that generally has increased cellularity and/or atypia (compared with a common nevus) and an increased (although generally still low) probability of neoplastic progression. A melanocytoma means forming a mass of neoplastic cells.

- Common mutations in each pathway are listed. Mutations already identified in benign or borderline low lesions are shown in bold.
- Blue, loss-of-function mutations; red, gain-of-function mutations; green, change-of-function mutations; orange, amplification; purple, rearrangement; grey, promoter mutation.
Multi-dimensional classification

- Sun exposure
- Context

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### Definitions:
- Melanocytoma: A tumorigenic neoplasm of melanocytes that generally has increased cellularity and/or atypia (compared with a common nevus) and an increased (although generally still low) probability of neoplastic progression. Tumorigenic means forming a mass of neoplastic cells.

### Table Notes:
- Common mutations in each pathway are listed. Mutations already identified in benign or borderline lesions are shown in bold.
- Blue, loss-of-function mutations; red, gain-of-function mutations; green, change of function mutations; orange, amplifications; purple, rearrangements; grey, promoter mutations.
Multi-dimensional classification

- Sun exposure
- Topography
- Morphology
Multi-dimensional classification

- Sun exposure
- Topography
- Morphological
- Genetics
Germline mutations (inherited)

Somatic mutations (acquired)
Genetic evolution of melanocytic tumours

Adapted from Yeh I/Bastian B
Genetic evolution of melanocytic tumours

Adapted from Yeh I/Bastian B
Post-zygotic mutations followed by Melanoblastic migration

Somatic mutations (acquired)

doi:10.1038/nature05660
Large congenital nevi
Exon 3 NRAS mutations
Plaque-type blue nevus
Exon 4 or 5 Gαq mutations
Molecular anomalies of Spitz tumours

- **HRAS** mutations (11p)
- Tyrosine kinase fusions
  - **ALK**
  - **ROS1**
  - **NTRK1**
  - **NTRK3**
  - **RET**
  - **MET**
- Serine-threonine kinase fusions
  - **BRAF**
Nevus Spilus
(HRAS G13R mosaicism)

Photo Dr Smulevici
4 step progression scheme of melanocytic tumors

**Nevus**

Single driver anomaly
4 step progression scheme of melanocytic tumors

Nevus
Single driver anomaly

«melanocytoma»
4 step progression scheme of melanocytic tumors

Nevus
Single driver anomaly

«melanocytoma»

«MelTUMP»
4 step progression scheme of melanocytic tumors

Nevus
Single driver anomaly

«melanocytoma»

«MelTUMP»

Melanoma
Multiple genomic alterations
4 step progression scheme of melanocytic tumors

Nevus
Single driver anomaly

«melanocytoma»

«MelTUMP»

Melanoma
Multiple genomic alterations
### Integrative classification of melanocytic tumours

<table>
<thead>
<tr>
<th>GNAQ, GNA11, PLCB4, CYSLTR2</th>
<th>BRAF, NRAS</th>
<th>HRAS, kinase fusions</th>
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<tbody>
<tr>
<td>Blue nevus, uveal nevus</td>
<td>Common nevus, Congenital nevus</td>
<td>Spitz Nevus</td>
</tr>
</tbody>
</table>

- **UV independent**
- **Non chronic sun-damage**
- **UV independent**
Integrative classification of melanocytic tumours

- **GNAQ, GNA11, PLCB4, CYSLTR2**
  - Blue nevus, uveal nevus

- **BRAF, NRAS**
  - Common nevus, Congenital nevus

- **HRAS, kinase fusions**
  - Spitz Nevus
Genetic evolution of melanocytic tumours

Normal melanocyte

Nevus

Intermediate Tumour “Melanocytoma”

Adapted from Yeh I
Integrative classification of melanocytic tumours

- **GNAQ, GNA11, PLCB4, CYSLTR2**
  - Blue nevus, uveal nevus
  - Cellular blue nevus

- **BRAF, NRAS**
  - Common nevus, Congenital nevus
  - Clonal nevus

- **HRAS, kinase fusions**
  - Spitz Nevus
  - Clonal Spitz tumor

Additionnal molecular anomalies

Adapted from Yeh I
Genetic evolution of melanocytic tumours

Normal melanocyte → Nevus → Melanocytoma → Intermediate Tumours
- MelTUMP
  - Atypical DPN
  - AST
  - IAMPUS

Adapted from Yeh I
Integrative classification of melanocytic tumours

- **GNAQ, GNA11, PLCB4, CYSLTR2**
  - Blue nevus, uveal nevus
  - Atypical blue nevus
  - MelTUMP

- **BRAF, NRAS**
  - Common nevus, Congenital nevus
  - Atypical nevus
  - MelTUMP

- **HRAS, kinase fusions**
  - Spitz Nevus
  - Atypical Spitz tumor
  - MelTUMP

Additional molecular anomalies

Adapted from Yeh I
Integrative classification of melanocytic tumours

- **GNAQ, GNA11, PLCB4, CYSLTR2**
  - Blue nevus, uveal nevus
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- **BRAF, NRAS**
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- **HRAS, kinase fusions**
  - Spitz Nevus
  - Atypical Spitz tumor
  - MelTUMP

Additional molecular anomalies

Adapted from Yeh I
Genetic evolution of melanocytic tumours

Normal melanocyte → Nevus → Melanocytoma → Intermediate Tumours (MelTUMP) → Melanoma

Adapted from Yeh I
Integrative classification of melanocytic tumours

- **GNAQ, GNA11, PLCB4, CYSLTR2**
  - Blue nevus, uveal nevus
  - Atypical blue nevus
  - Blue type melanoma, Uveal melanoma

- **BRAF, NRAS**
  - Common nevus, Congenital nevus
  - Atypical nevus
  - NRAS, BRAF mutated melanoma

- **HRAS, kinase fusions**
  - Spitz Nevus
  - Atypical Spitz tumor
  - Malignant Spitz Tumour

Additional molecular anomalies

Adapted from Yeh I
Progression of Spitz lesions

- Spitz nevus
- Atypical Spitz nevus (melanocytoma)
- Atypical Spitz nevus (melTUMP)
- Malignant Spitz tumour
Atypical Spitz tumour

Spitz nevus

Spitz progression

MelTUMP

Malignant Spitz tumour
Integrative classification of melanocytic tumours

- Common nevus, Congenital nevus
- Spitz Nevus
- Blue nevus, uveal nevus
- Atypical blue nevus
- Atypical nevus
- Atypical Spitz tumor
- Blue type melanoma, Uveal melanoma
- NRAS, BRAF mutated melanoma
- Malignant Spitz Tumour

Adapted from Yeh I
«Focused, small data » research
Research project

- Exploring **morpho-genetic correlations** in melanocytic tumors

![Driver alteration chart](chart.png)
Research project
Clinical endpoints

• Better classification

<table>
<thead>
<tr>
<th>Driver alteration</th>
<th>Primary alteration</th>
</tr>
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<tbody>
<tr>
<td>BRAF</td>
<td>20</td>
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<tr>
<td>NRAS</td>
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</tr>
<tr>
<td>HRAS</td>
<td>5</td>
</tr>
<tr>
<td>PRKAR1A</td>
<td>1</td>
</tr>
<tr>
<td>MAP2K1</td>
<td>0</td>
</tr>
<tr>
<td>c-kit</td>
<td>0</td>
</tr>
<tr>
<td>NF1</td>
<td>0</td>
</tr>
<tr>
<td>GNAQ/GNA11</td>
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</tr>
<tr>
<td>BRAF-fusion</td>
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<td>ALK-fusion</td>
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<td>NTRK1-fusion</td>
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<td>ROS1-fusion</td>
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<td>PRKCA-fusion</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>20</td>
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</table>
Research project
Clinical endpoints

• Better classification

• Optimized treatment:
  - Reduce over-treatment of unclassified benign tumors
  - Personalized therapy in malignant cases
Focused small data research

Molecular pathologist focused on a small segment of diagnosis
Focused small data research

Molecular pathologist focused on a small segment of diagnosis

« Stacking effect » of unclassified cases
What does rare unclassified cases mean?
A small percentages of all cases are sent for expert review by the general pathologist (3%)
The expert is unable to classify a few cases
In order to progress in the classification of tumours these cases must be analysed by new techniques when available.
« Needlestack » phenomenon

Stack of unclassified cases with almost no regular type of melanocytic tumors.
« Needlestack » phenomenon

The job is not to « find a needle in a haystack » but to sort-out different types of needles in a needlestack

Drawing reproduced with permission of author (Frits Ahlefeldt)
Looking for known unknowns

Driver alteration

- BRAF
- NRAS
- HRAS
- PRKAR1A
- MAP2K1
- c-kit
- NF1
- GNAQ/GNA11
- BRAF-fusion
- ALK-fusion
- NTRK1-fusion
- ROS1-fusion
- RET-fusion
- MET-fusion
- NTRK3-fusion
- PRKCA-fusion
- Unknown
Low chance of finding new major drivers to fill all the gaps
High chance of finding numerous new drivers with low frequency.
Best to aim for an «in between» model
Melanoledge project
Integrative analysis

Embryogenesis

Clinical features

Microscopy/morphology

Immunophenotype

Genomic profile

Mutation status

Methylation profiles

Clinical evolution
Melanoledge project
Integrative analysis

Embryogenesis
Clinical features
Microscopy/morphology
Immunophenotype
Genomic profile
Mutation status
Methylation profiles
Clinical evolution
items below 2 removed. 16520 items left. Expdata has 1652 items after IQR (threshold: 1.07) filtering.

#kudos@FTirode
t-Distributed Stochastic Neighbor Embedding
tSNE
Looking for known unknowns

- Once you identify a new pattern you will expand the numbers to confirm this pattern but this will not help you find other lesions with a different pattern so you need to expand your research to a group:

  ie global unclassified multi-entity screening process
Looking for known unknowns

• Once you identify a new pattern you will expand the numbers to confirm this pattern but this will not help you find other lesions with a different pattern so you need to expand your research to a group: ie global unclassified multi-entity screening process

• Discovery of morphological differential diagnoses (unknown unknowns)
Looking for known unknowns

• Once you identify a new pattern you will expand the numbers to confirm this pattern but this will not help you find other lesions with a different pattern so you need to expand your research to a group: ie global unclassified multi-entity screening process

• Discovery of morphological differential diagnoses (unknown unknowns)

• Data mining can lead to finding morphologically-unrelated entities sometimes in other organs
Inter-organ common cancer genetics

Melanoma

ALK fusion
ROS1 fusion
NTRK1 fusion

Thyroid cancer

ALK fusion
ROS1 fusion
NTRK1 fusion

Lung ADK

ALK fusion
ROS1 fusion
NTRK1 fusion
Inter-organ common cancer genetics

Melanoma
- ALK fusion
- ROS1 fusion
- NTRK1 fusion
- New fusion

Thyroid cancer
- ALK fusion
- ROS1 fusion
- NTRK1 fusion

Lung ADK
- ALK fusion
- ROS1 fusion
- NTRK1 fusion
Inter-organ common cancer genetics

Melanoma
- ALK fusion
- ROS1 fusion
- NTRK1 fusion
- New fusion

Thyroid cancer
- ALK fusion
- ROS1 fusion
- NTRK1 fusion
- New fusion?

Lung ADK
- ALK fusion
- ROS1 fusion
- NTRK1 fusion
- New fusion?
Inter-organ common cancer genetics

Melanoma
- ALK fusion
- ROS1 fusion
- NTRK1 fusion
- New fusion

Thyroid cancer
- ALK fusion
- ROS1 fusion
- NTRK1 fusion
- New fusion?

Lung ADK
- ALK fusion
- ROS1 fusion
- NTRK1 fusion
- New fusion?

Other Organs/Tumors
- ?

New fusion?
Giant congenital nevus
What about the <1%?
Giant congenital nevus
What about the <1%?

• Approximately 1/50 Million births
Giant congenital nevus
What about the <1%?

• Approximately 1/50 Million births : <3 cases/year worldwide
Giant congenital nevus
What about the <1%?

3 different undescribed anomalies (gene fusions)
- Whole exome RNAseq/clustering/TSNE analysis
- Array-CGH
- Designed FISH break-apart probes
New findings: KITSG-NFKD rearrangement
New findings: *KITSG-NFKD rearrangement*

- KITSG: Known Inactivated Tumour Suppresser Gene
- NFKD: New Functional Kinase Domain
Giant congenital nevus
What about the <1%?

- 3 different undescribed anomalies (including public databases)
Giant congenital nevus
What about the <1%?

• 3 different undescribed anomalies (including public databases)
• 3 different microscopic patterns (entry point for cohort expansion)
Giant congenital nevus
What about the <1%?

• 3 different undescribed anomalies (including public databases)
• 3 different microscopic patterns (entry point for cohort expansion)
• Through morphology-based prospective screening we were able to find both non-giant and/or transformed variants of all 3 new genetic subtypes
Example n°1
F2, congenital lesion
Slowly growing nodule removed at 14mo
Deep area
MyoD1
SASS6-RAF1 fusion identified

CAGCCACCCCTGGTTGAGGAACAAAG | GATGCAATTTCGAAGTCACAGCGAAT

SASS6_ENST00000287482_(e14)-RAF1_ENST00000251849_(e8)
RAF1 Break-apart FISH probe

Nevus area
RAF1 Break-apart FISH probe

Melanoma area
Gene expression profile clustering with RMS
Gene expression profile clustering with melanomas
Case synthesis

- *SASS6-RAF1* is a new fusion transcript in giant congenital nevus
- Early malignant transformation with metastatic dissemination
- First description of RMS in melanoma ex-giant congenital nevus
- Clustering data suggested full redifferentiation in RMS component
Complexity of combinatory models in advanced tumors

• Redundant sequences of secondary events in tumorogenesis
• Sometimes mutually exclusive
• Specific morphology linked to the combination of 2 genetic alterations
Complexity of combinatory models in advanced tumors

• Redundant sequences of secondary events in tumorogenesis
• Sometimes mutually exclusive
• Specific morphology linked to the combination of 2 genetic alterations
Turning data into tumor classification and decision helping algorithms

- Embryogenesis
- Clinical features
- Microscopy/morphology
- Immunophenotype
- Genomic profile
- Mutation status
- Methylation profiles
- Clinical evolution

❖ Suggested classifying anomaly
❖ Suggested staging anomalies
❖ Suggested treatments
Example n°2
Molecular anomalies of Spitz tumours

• HRAS mutations (11p)
• Tyrosine kinase fusions
  • ALK
  • ROS1
  • NTRK1
  • NTRK3
  • RET
  • MET
• Serine-threonine kinase fusions
  • BRAF
Molecular anomalies of Spitz tumours

• *HRAS* mutations (11p)

• Tyrosine kinase fusions
  • *ALK*
  • *ROS1*
  • *NTRK1*
  • *NTRK3*
  • *RET*
  • *MET*

• Serine-threonine kinase fusions
  • *BRAF*

Still many cases that were negative
Molecular anomalies of Spitz tumours

• *HRAS* mutations (11p)
• Tyrosine kinase fusions
  • *ALK*
  • *ROS1*
  • *NTRK1*
  • *NTRK3*
  • *RET*
  • *MET*
• Serine-threonine kinase fusions
  • *BRAF*

Still many cases that were negative

Research focus
Multiple unknown « in frame » fusion in unclassified case

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MAP3K8 fusions

• At one point we realized we had 6 cases with a similar MAP3K8 fusion in the cluster
MAP3K8 fusions

- At one point we realized we had 6 cases with a similar MAP3K8 fusion in the cluster

- Morphological analysis with identification of features allowing a more efficient search of new cases
4 step progression scheme of melanocytic tumors

1. Nevus
2. « melanocytoma »
3. « MelTUMP »
4. Melanoma
4 step progression scheme of melanocytic tumors

- Nevus
- « melanocytoma »
- « MelTUMP »
- Melanoma
MAP3K8 fusions

• At one point we realized we had 6 cases with a similar MAP3K8 fusion in the cluster

• Morphological analysis with identification of features allowing a more efficient search of new cases

• Development of screening tools (FISH break-apart probe, IHC, aCGH)
Predominant anomaly **MAP3K8-SVIL**

- Both genes on chromosome 10p and adjacent
MAP3K8 expression was significantly higher in MAP3K8-fused cases/ other Spitz fusions
MAP3K8 FISH Break-Apart probe
N-term MAP3K8 IHC
Penetrance plot of 12 aCGH
MAP3K8 fusions

• At one point we realized we had 6 cases with a similar MAP3K8 fusion in the cluster
• Morphological analysis with identification of features allowing a more efficient search of new cases
• Development of screening tools (FISH break-apart probe, IHC)
• Collaboration UCSF
• Currently >40 cases with a publication including 33 cases
Activating Structural Alterations In MAPK Genes Are Distinct Genetic Drivers In a Unique Subgroup Of Spitzoid Neoplasms

Victor L. Quan, BA,* Bin Zhang, MS,* Lauren S. Mohan, MSc,* Katherine Shi, BS,* Maria C. Isales, MD, MPH,† Elnaz Panah, MD,* Timothy J. Taxter, MD,† Nike Beaubier, MD,† Kevin White, PhD,‡ and Pedram Gerami, MD*

Abstract: Recent studies have described kinase fusions as the most common initiating genomic events in Spitzoid neoplasms. Each rearrangement generates a chimeric protein with constitutive activation

Key Words: Spitzoid, Spitzoid melanoma, atypical Spitz tumor, fusions, genomics, MAP3K8, MAP3K3, MAP2K1

(Am J Surg Pathol 2019;00:000–000)
Clinical genome sequencing uncovers potentially targetable truncations and fusions of MAP3K8 in spitzoid and other melanomas

Scott Newman1*, Liying Fan2, Allison Pribnow3,4, Antonina Silkov1, Stephen V. Rice1, Seungjae Lee5, Ying Shao1, Bridget Shaner1, Heather Mulder1, Joy Nakitandwe5, Sheila Shurtleff5, Elizabeth M. Azzato5, Gang Wu1, Xin Zhou1, Raymond Barnhill6, John Easton1, Kim E. Nichols3, David W. Ellison5, James R. Downing5, Alberto Pappo3, Philip M. Potter2, Jinghui Zhang1* and Armita Bahrami3,5*
C-terminal truncation of MAP3K8 results in increased kinase-specific activity
C-terminal truncation of MAP3K8 results in increased kinase-specific activity
MAP3K8 activation can result either from truncating mutations or rearrangements.

Diagram:
- N-term
- Kinase domain
- C-term regulatory region

- N-term
- Kinase domain
- «Stop-Codon» truncating mutation
MAP3K8 activation can result either from truncating mutations or rearrangements.
New findings: *KITSG-NFKD rearrangement*

- **KITSG**: Known Inactivated Tumour Suppressor Gene
- **NFKD**: New Functional Kinase Domain
New findings: KITSG-NFKD rearrangement

- KITSG: Known Inactivated Tumour Suppressor Gene
- NFKD: New Functional Kinase Domain

« Out of the box » thinking

Dogmatism Research Progress
Molecular anomalies of Spitz tumours

- **HRAS** mutations (11p)
- Tyrosine kinase fusions
  - **ALK**
  - **ROS1**
  - **NTRK1**
  - **NTRK3**
  - **RET**
  - **MET**
- Serine-threonine kinase fusions
  - **BRAF**
  - **MAP3K8**
  - **MAP3K3**
Best to aim for an « in between » model

- Molecular driver
  - MAP3K8
  - MAP3K3

Legend:
- Known
- New1
- New2
- New3
- New4
- New5
- New6
- New7
- New8
- New9
- New10
Inter-organ common cancer genetics

Melanocytes
- ALK fusion
- ROS1 fusion
- NTRK1 fusion
- New fusion

Thyroid cancer
- ALK fusion
- ROS1 fusion
- NTRK1 fusion
- New fusion?

Lung ADK
- ALK fusion
- ROS1 fusion
- NTRK1 fusion
- New fusion?

Other Organs/Tumors
- New fusion?
Inter-organ common cancer genetics

Melanocytes
- ALK fusion
- ROS1 fusion
- NTRK1 fusion
- MAP3K8 fusion

Thyroid cancer
- ALK fusion
- ROS1 fusion
- NTRK1 fusion
- MAP3K8 fusion

Lung ADK
- ALK fusion
- ROS1 fusion
- NTRK1 fusion
- MAP3K8 fusion

Ovarian ADK
Colon ADK
Mesothelioma

MAP3K8 fusion
MAP3K8 is present on the Nanostring gene list since 2019
MAP3K8 is absent of the Foundation one gene list.
Example n°3
M82, lumbar area
Slowly growing for $2^{1/2}$ years

12mm enucleated dermal nodule
Re-excision specimen: strictly dermal nodule
Suggested diagnosis: metastatic melanoma?
Suggested diagnosis: metastatic melanoma?

• No primary found by extensive work-up
Suggested diagnosis: metastatic melanoma?

- No primary found by extensive work-up
- CGH: no visible anomaly
Suggested diagnosis: metastatic melanoma?

• No primary found by extensive work-up
• CGH

• **NGS** 49 cancer gene panel including **BRAF, NRAS, MAP2K1, HRAS, TP53, GNAQ, GNA11** and **hTERT** promoter region: no mutations
Suggested diagnosis: metastatic melanoma?

• No primary found by extensive work-up
• CGH
• NGS 49 cancer gene panel including \textit{BRAF}, \textit{NRAS}, \textit{MAP2K1}, \textit{HRAS}, \textit{TP53}, \textit{GNAQ}, \textit{GNA11} and \textit{hTERT} promoter region: no mutations
• Spitz fusion IHC screening (ALK, NTRK1, ROS1)
NTRK1 IHC
NTRK1 Break-apart FISH
RNA-sequencing
CRTC1 fusion in big data
CRTC1-MAML2 fusion well known
TRIM11 fusion in big data?
**CRTC1-TRIM11** Melanocytoma morphology

**Cellular pleomorphism**

**Exceptionnal pigmented cells**
Confirmation tools

• Designed *TRIM11* FISH Break-apart probe
Confirmation tools

- Designed *TRIM11* FISH Break-apart probe
- TRIM11 antibody targeting the C-terminal end of the protein
Confirmation tools

• Designed TRIM11 FISH Break-apart probe
• TRIM11 antibody targeting the C-terminal end of the protein
Cutaneous Melanocytoma With CRTC1-TRIM11 Fusion

Report of 5 Cases Resembling Clear Cell Sarcoma

Lucie Cellier, MD,* Emilie Perron, MD, MSc,*†‡ Daniel Pissaloux, PhD,*
Marie Karanian, MD,* Veronique Haddad, PharmD,* Laurent Alberti, PhD,*
and Arnaud de la Fouchardièreme, MD, PhD*
Differential Diagnosis

• Metastatic melanoma
Differential Diagnosis

- Metastatic melanoma (history+++)
Differential Diagnosis

- Metastatic melanoma
- Clear cell sarcoma
Am J Surg Pathol 2010 34; 216-222 Hantschke et coll
EWSR1 Break-apart FISH technique

Allows identification of EWSR1-ATF1, EWSR1-CREB1 and EWSR1-CREM fusions
Entities with similar morphology published in the literature

• Primary dermal melanoma

Solitary Melanoma Confinned to the Dermal and/or Subcutaneous Tissue: Evidence for Revisiting the Staging Classification

Bowen, Glen M. MD; Chang, Alfred E. MD; Lowe, Lori MD; Hamilton, Ted MS; Patel, Rupa BA; Johnson, Timothy M. MD

Arch Derm 1999
Entities with similar morphology published in the literature

- Primary dermal melanoma

Swetter at al Arch Derm 2004
Entities with similar morphology published in the literature

- Primary dermal melanoma
- Paraganglioma–like dermal melanocytic tumor

F46 back

• Case sent from Dr Marc Haspeslagh (Gent)
• Primary tumor
• \textit{EWSR1} FISH negative
• \textit{CRCT1-TRIM11} cutaneous melanocytoma?
Array-CGH

• Multiple segmental gains and losses
RNA seq *TFG-ETV5* (in frame)

- *TFG* 3q12.2 Trk fused gene
- *ETV5* 3q27 (FOXM1 transcription factor network)
- Both gene already involved in fusions in other malignancies
Another potential new entity

• Primary dermal melanoma with $TFG-ETV5$ fusion
Another potential new entity

• Primary dermal melanoma with TFG-ETV5 fusion
• Discovery of an « unknown unknown »
Melanocytoma with \textit{CRTC1-TRIM11} fusion

- Currently expanding our series
- Now 14 cases including 3 young patients (12 y-o)
- Nearly every reviewed CCS-like cutaneous tumor EWSR1- reclassified
- New morphological aspects:
  - Exophytic nodules
  - Junctional nests
CRTC1-TRIM11 fusion defined melanocytic tumors: A series of four cases.

Ko JS1, Wang L1, Billings SD1, Pissaloux D2,3, Tirole F3, Berry R1, De La Fouchardière A2,3.

Author information
1 Department of Pathology, Cleveland Clinic, Cleveland, Ohio.
2 Department of Pathobiology, Centre Léon Bérard, Lyon, France.
3 Univ Lyon, Université Claude Bernard Lyon 1, Research Cancer Center of Lyon, Lyon, France.

CRTC1-TRIM11 Fusion in a Case of Metastatic Clear Cell Sarcoma: Are CRTC1-TRIM11 Fusion-bearing Tumors Melanocytomas or Clear Cell Sarcomas?

Bontoux C1, Baroudjian B2, Le Maignan C3, Vercellino L4, Farges C5, Guillemot D6, Pierron C6, Lebbé C2,7, Battistella M1,8.

Author information
1 Departments of Pathology.
2 Dermatology.
3 Oncology.
4 Nuclear Medicine.
5 Radiology, Hôpital Saint-Louis, APHP.
6 Department of Genetics, Institut Curie, PSL Research University.
7 INSERM UMR_S976.
8 INSERM UMR_S1165, Paris 7 University, Paris, France.
A case report of cutaneous melanocytoma with CRTC1-TRIM11 fusion: Is CMCT distinct from clear cell sarcoma of soft tissue?

Kashima J¹, Motoi T¹, Nishimaki M², Hayashi Y¹, Ogawa M¹, Kato I¹, Yamada R¹, Tonooka A¹, Horiguchi S¹, Funata N¹, Hishima T¹, Yoshino K².

Author information
1. Department of Pathology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan.
2. Department of Dermatologic Oncology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan.
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Current Gene List

Genes with full coding exonic regions included in FoundationOne®CDx for the detection of substitutions, insertion–deletions (indels), and copy-number alterations (CNAs).
Molecular findings in melanocytic tumors final comments

• Molecular pathology is on a fast paced evolution path
Molecular findings in melanocytic tumors
final comments

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final comments

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• Trend is to go from complex to widely accessible techniques (IHC)
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• Morphology is the best screening tool

• Follow-up studies with genetics are currently needed to reach the next level of clinical management
Focused small data research: pros and cons

• **Pros:**
  - Efficient
  - Low budget
  - Immediately transferable to diagnosis

• **Cons:**
  - Rarity of expert centers that can potentially perform it (cases+TK+$)
  - No basic research structure associated
  - Slow publishing rate (*ie* too many discoveries)
  - Needs confirmation in larger groups
What « Small focused data research » brings to the table:

• Effective model to enhance classification by reducing the group of unknown in benign, atypical and malignant cases
• Potential transversal discoveries
• Personalized medecine treatment options in the <1% frequency
• Morphology is a strong axe of correlation (AI)
Gene fusions : food for thought

• Little knowledge of their origin (when and how?)
• What makes them different from a mutation?
• Importance of both partners?
Many thanks to my team