Microtubule-based Cancer Therapeutics

BIOS-010
September 12, 2018

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PhD Candidate
Cassimeris Lab
What are microtubules? Why target them in cancer therapy?

How do microtubule-based cancer therapies work?  
What is Taxol?

What are the clinical limitations or implications of microtubule-targeting drugs?
Microtubules are a component of the cytoskeleton
Microtubules exhibit dynamic instability
Microtubules are also critical to cell division.
MT dynamics essential to sister chromatid segregation
Preventing cell division to target over-proliferation
Rationale behind microtubule-targeting drugs

**microtubule stabilizers**
[paclitaxel (Taxol™)]

**microtubule depolymerizers**
[vinblastine, colchicine]
Rationale behind microtubule-targeting drugs

microtubule stabilizers
[paclitaxel (Taxol™)]

microtubule depolymerizers
[vinblastine, colchicine]
**Classes of tubulin-targeting drugs**

**Microtubule Stabilizers**

- [Paclitaxel (Taxol™)]
  - Promote MT growth
  - Stabilize MTs
  - Increase MT polymer mass

**Microtubule Depolymerizers**

- [Vinblastine, Colchicine]
  - Prevent MT growth
  - Destabilize MTs
  - Decrease MT polymer mass
Anti-mitotic mechanism of microtubule-targeting drugs

**microtubule stabilizers**
[paclitaxel (Taxol™)]

**microtubule depolymerizers**
[vinblastine, colchicine]

mitotic block

cell death

apoptosis (programmed cell death)
Taxol is a successful cancer therapy

Taxol discovery timeline:

- 1960: 1st bark collected
- 1970: Toxicity discovered
- 1980: Experimental anti-cancer tests promising
- 1980: MT-stabilizing mechanism described
- 1990: Phase 1 & 2
- 1990: NCI partners with BMS
- 2000: BMS annual sales $1.6 billion
- 2010: 1st insight into molecular pathway activating apoptosis
Taxol is a successful cancer therapy

Taxol discovery timeline:

• Treats several types of cancer: ovarian, breast, lung, Kaposi sarcoma, cervical, pancreatic

• Treated over 1 million patients within first 10 years since approval (BMS)

• Continued success: WW sales ~$105 million (2015); ~$90 million (2016) (Evaluate Group)
**Taxol inhibits microtubule dynamic instability**

Control

![Control](image)

30nM Taxol

![30nM Taxol](image)

**Taxol inhibits MT dynamics**

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>Control</th>
<th>+Taxol</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
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</tr>
<tr>
<td>100</td>
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</table>

Relative distance (µm)
Taxol causes defects in spindle assembly
Reorganization of the MT array at mitotic entry
Microtubules reorganize at the start of mitosis

Interphase → Mitosis

~5 min
Dynamics facilitate reorganization of the MT array
Dynamics at NEBD favors MT shortening to clear array

Interphase:
- Grow (catastrophe promoting)
- Shorten (rescue promoting)

Entering Mitosis:
- Grow (catastrophe promoting)
- Shorten (rescue promoting)
Dynamics at NEBD favors MT shortening to clear array

Interphase

catastrophe → grow
rescue ← shorten

Taxol

catastrophe → grow
rescue ← shorten

Entering Mitosis

catastrophe → grow
rescue ← shorten

rescue promoting
catastrophe promoting
rescue promoting
catastrophe promoting
rescue promoting
catastrophe promoting
Taxol should prevent entry to mitosis...
Taxol should prevent entry to mitosis... but does not

Therein, lies the conundrum of how cells respond to Taxol
Theoretical vs. actual cell cycle block in Taxol

**Taxol**

catastrophe → shorten
rescue ←

**Theoretical cell cycle block**

G2  M
Theoretical vs. actual cell cycle block in Taxol
Taxol’s MT-stabilizing activity is antagonized at mitotic entry
**Taxol-treated cells exhibit a unique pattern of interphase MT array clearing**

Control

Taxol
Taxol-treated cells exhibit a unique pattern of interphase MT array clearing.
Why are Taxol-stabilized arrays sensitive to depolymerization specifically at the G2/M transition?

What are the players that can “beat” Taxol?

Why now?
Department of Biological Sciences
Colloquium Seminar Series

Jessica Leung
PhD Candidate, Nemes Fellow
Department of Biological Sciences, Lehigh University

Thursday, September 27, 2018
Iacocca Hall, B-023
4:10 PM
Clinical limitations of Taxol (& other MTAs)

- Toxicity and side effects
  - Hematological (blood) toxicity
  - Neurotoxicity, neuropathy
Clinical limitations of Taxol (& other MTAs)

- Drug resistance
  - Specific tubulin isotypes
  - Altered microtubule dynamics
  - Mutations to cell death pathway
  - Membrane pumps and drug efflux

apoptosis (programmed cell death)
MT-associated proteins (MAPs) as potential drug targets

• Many MAPs have critical roles during cell division

• Objective: Induce mitotic arrest, without affecting MT dynamics
  • Efficacy of Taxol, without toxicities
**MT-associated proteins (MAPs) as potential drug targets**

### Mitotic MAPs

<table>
<thead>
<tr>
<th>Kinesin</th>
<th>Hits or lead compounds</th>
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<tbody>
<tr>
<td>KIF2A⁺</td>
<td></td>
</tr>
<tr>
<td>KIF2B</td>
<td></td>
</tr>
<tr>
<td>MCAK</td>
<td>Sulfoquinovosylglycerol inhibitors [REF. 88]</td>
</tr>
<tr>
<td>KIF4A⁺ and KIF4B⁺</td>
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</tr>
<tr>
<td>CENPE</td>
<td>GSK923295 [REF. 49]</td>
</tr>
<tr>
<td>EG5⁺</td>
<td>Ispinesib-like and several others</td>
</tr>
<tr>
<td>KIF14</td>
<td></td>
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<tr>
<td>KIF15</td>
<td>Quinazolinedione and phthalimide inhibitors [REF. 173]</td>
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<tr>
<td>KIF18A</td>
<td>BTB1 [REF. 108]</td>
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<tr>
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<tr>
<td>MKLP1⁺</td>
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<tr>
<td>MKLP2</td>
<td>Paprotrain [REF. 175]</td>
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<tr>
<td>MPP1</td>
<td>2-phenyl-quinoxalines [REF. 208]</td>
</tr>
<tr>
<td>KID</td>
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<td>HSET</td>
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### MAP inhibitors in clinical development

<table>
<thead>
<tr>
<th>Kinesin target</th>
<th>Inhibitor</th>
<th>Company</th>
<th>Clinical phase</th>
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<tr>
<td>EG5</td>
<td>Ispinesib</td>
<td>Cytokineti(cs</td>
<td>II</td>
</tr>
<tr>
<td>AZD4877</td>
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<td>AstraZeneca</td>
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<td>ArQule</td>
<td>I</td>
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<td>Kyowa Hakko Kirin/Eli Lily</td>
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<td>4SC AG</td>
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<tr>
<td>MPP1</td>
<td>Peptide</td>
<td>Shiga University</td>
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Potential implication of anti-mitotic drugs

- Selection for “slow-growers”/“non-dividers”
  - Cancer stem cells

![Diagram showing normal and cancer cells with and without anti-mitotic drug addition.]
Microtubules are part of the cytoskeleton & play an essential role in mitosis

Microtubule-based cancer therapies target dynamic instability & act as anti-mitotic agents

Taxol is a microtubule-stabilizing drug & successful cancer therapy

Clinical limitations: Side effects/toxicity, drug resistance, selection for slow/non-dividing cells