Developing a sustainable source of Canada yew biomass for drug production: Plantation research in Ontario
Thomas Noland, Mamdouh Abou-Zaid, Ron Smith, and Stew Cameron
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Acknowledgements

Yew Talk Outline

- Canada Yew background
- Canada Yew research project with preliminary results
- Summary

Canada Yew Background

- Canada yew evergreen shrub native to N. Amer.
- Height + spread 1.5 m
- Sweeping form to branches

Medicinal Properties of Yew

- Yew contains paclitaxel and two other potential anticancer compounds 10-DAB and DHB (unique to Canada yew) in its foliage, bark, & roots
- Paclitaxel is the active ingredient in Taxol™ an anticancer drug sold by Bristol-Myers-Squibb (BMS)
- Taxol™ is one of the world’s most valuable anticancer drugs -9 billion $US sales for BMS1993-2002
- Paclitaxel is also produced from English and Asian species of yew

Paclitaxel Uses and Activity

- Taxol® is a chemotherapy drug registered for use on ovarian, breast, and non-small lung cancer.
- Paclitaxel coated coronary stents (Boston Sci.)
- Abraxane new form of taxol approved by FDA, may increase its usage in breast cancer treatment
- 28 % of ’00 cancer clinical trials used taxanes
- Trials being conducted for taxane use in psoriasis, rheumatoid arthritis, multiple sclerosis, and fungal and viral diseases
Taxane Demand and Production

- Current worldwide taxane is ↑ at ~ 10% year
- 2006 demand was about 750 kg
- 15,000 kg foliage to extract 1 kg paclitaxel
- 11.3 million kg of foliage/yr for world supply in 2006
- 1 ha wild Canada yew produces from 90 to 400 kg foliage every 4th year (sustainably harvested)

Canada Yew Research Project

- “Canada Yew: Developing a new value added crop for Northern Ontario”
- Objectives:
  - To develop a northern Ontario source for cutting-propagated Canada yew plants.
  - To develop methods to grow Canada yew as a new crop for northern Ontario growers
  - To develop methods to maximize paclitaxel yield of yew.

Yew Project Partners

- Thessalon First Nation BioCentre Nursery
- CFS-GLFC, Dr. Mamdouh Abou-Zaid
- CFS-AFC, Drs. R. Smith and S. Cameron
- Forest and Land Control, Blind River, ON
- Whelan Resources, Brian Whelan
- Bioxel Pharma
- ULERN
- MNR Bondar, Dr. Michael Irvine

Why Canada yew?

<table>
<thead>
<tr>
<th>Taxane content of yew species</th>
<th>Species</th>
<th>Pacilitaxel</th>
<th>Baccatin III</th>
<th>Total Taxanes mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. wallichiana</td>
<td>266</td>
<td>230</td>
<td>166</td>
<td>662</td>
</tr>
<tr>
<td>T. x media cv.</td>
<td>104</td>
<td>63</td>
<td>41</td>
<td>208</td>
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<tr>
<td>T. x hunnewalania</td>
<td>1,996</td>
<td>1395</td>
<td>168</td>
<td>433</td>
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<tr>
<td>T. globosa</td>
<td>2,205</td>
<td>1689</td>
<td>168</td>
<td>467</td>
</tr>
<tr>
<td>T. floridana</td>
<td>240</td>
<td>120</td>
<td>15</td>
<td>105</td>
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<tr>
<td>T. cuspidata</td>
<td>96</td>
<td>70</td>
<td>26</td>
<td>192</td>
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<td>T. canadensis</td>
<td>3,174</td>
<td>2665</td>
<td>224</td>
<td>335</td>
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<tr>
<td>T. brevifolia</td>
<td>467</td>
<td>41</td>
<td>296</td>
<td>764</td>
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<td>T. baccata</td>
<td>817</td>
<td>762</td>
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<td>1,603</td>
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<td>T. celebica</td>
<td>43</td>
<td>10</td>
<td>105</td>
<td>158</td>
</tr>
</tbody>
</table>

Why Plantations?

- Why not synthesize paclitaxel?
- Why not produce all paclitaxel through tissue culture?

Approach to Maximizing Paclitaxel Yield of Yew

- Screening 300 yew plants for growth and paclitaxel concentration
- Investigating growing conditions to optimize growth and paclitaxel content
- Choosing harvest time to maximize paclitaxel content

Why not synthesize paclitaxel?

Why not produce all paclitaxel through tissue culture?
Selecting Yew for Paclitaxel Production

- Cuttings collected from 300 individual plants across northern Ontario
- Propagated at OFRI greenhouse and planted at arboretum
- Each monitored for paclitaxel and growth
- Best growth + paclitaxel individuals selected for further propagation

Greenhouse Growth of Individuals

<table>
<thead>
<tr>
<th>Region</th>
<th>Algoma RL</th>
<th>Neast</th>
<th>Algoma LWR</th>
</tr>
</thead>
<tbody>
<tr>
<td># of new shoots</td>
<td>3.2</td>
<td>11.0</td>
<td>28</td>
</tr>
<tr>
<td>New shoot growth mm</td>
<td>115</td>
<td>387</td>
<td>733</td>
</tr>
<tr>
<td>Growth Response</td>
<td>Lowest</td>
<td>Average</td>
<td>Maximum</td>
</tr>
</tbody>
</table>

Greenhouse Growth of Yew Plants

Plantations Established

- June 2004 – CFS plantation at OFRI arb
- August 2005
  - OFRI arboretum (loamy soil)
  - Thessalon First Nation BioCentre (sandy soil)
  - Brian Whelan Farm, Thessalon (clay soil)
- Treatments:
  - Fertilizer, mulch, Fert+mulch (CFS: compost + compost and mulch)
  - Spacing 30 + 45 cm
  - Herbicide trials with Princep and Goal

Treatment effects on Yew Growth

Taxane Production Index

- Low
- High
- Algoma
- NE ON
- NW ON
Canada Yew Talk Summary

- Elite plantations will likely be one of the preferred taxane source of the future
- Plantation development will require 4 years for one time harvest or 5-8 years for continuous harvest
- Ontario-adapted elite material could lead to future plantations for 2nd generation taxane drug production (taxotere and abraxane)