Targeting the Notch Pathway: Killing Cancer Stem Cells

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Frontiers of Chemistry

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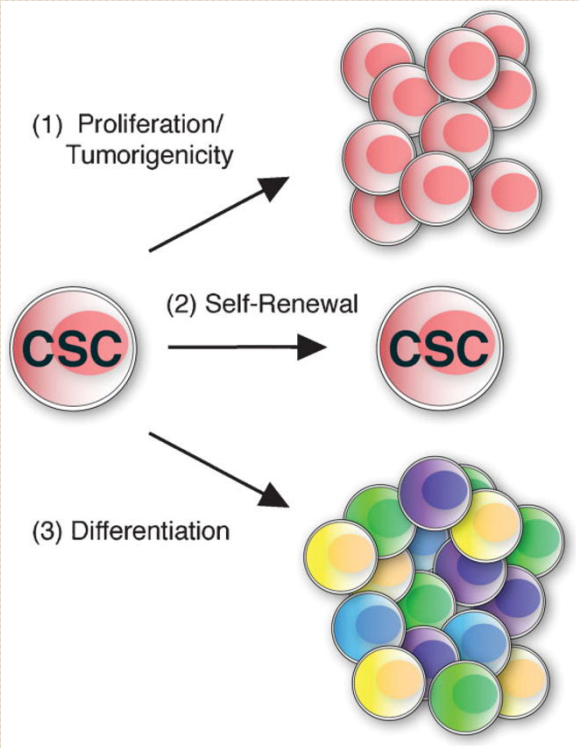
Outline

- Background
  - Cancer Stem Cells
  - The Notch Pathway
- Targeting agents
  - Drugs
  - Antibodies
- Challenges
- Future Directions
- Conclusions

Cancer Stem Cells

- Definition: Cells within a tumor that possess the capacity for ***self-renewal***, ***differentiation***, and ***tumorigenesis*** when implanted into an animal host
- First identified in 1994 in human acute myeloid leukemia (AML)
  - Cells were transplanted into severe combined-immune deficient (SCID) mice and tumors formed
- Found for first time in human solid tumors (breast, brain) in 2003

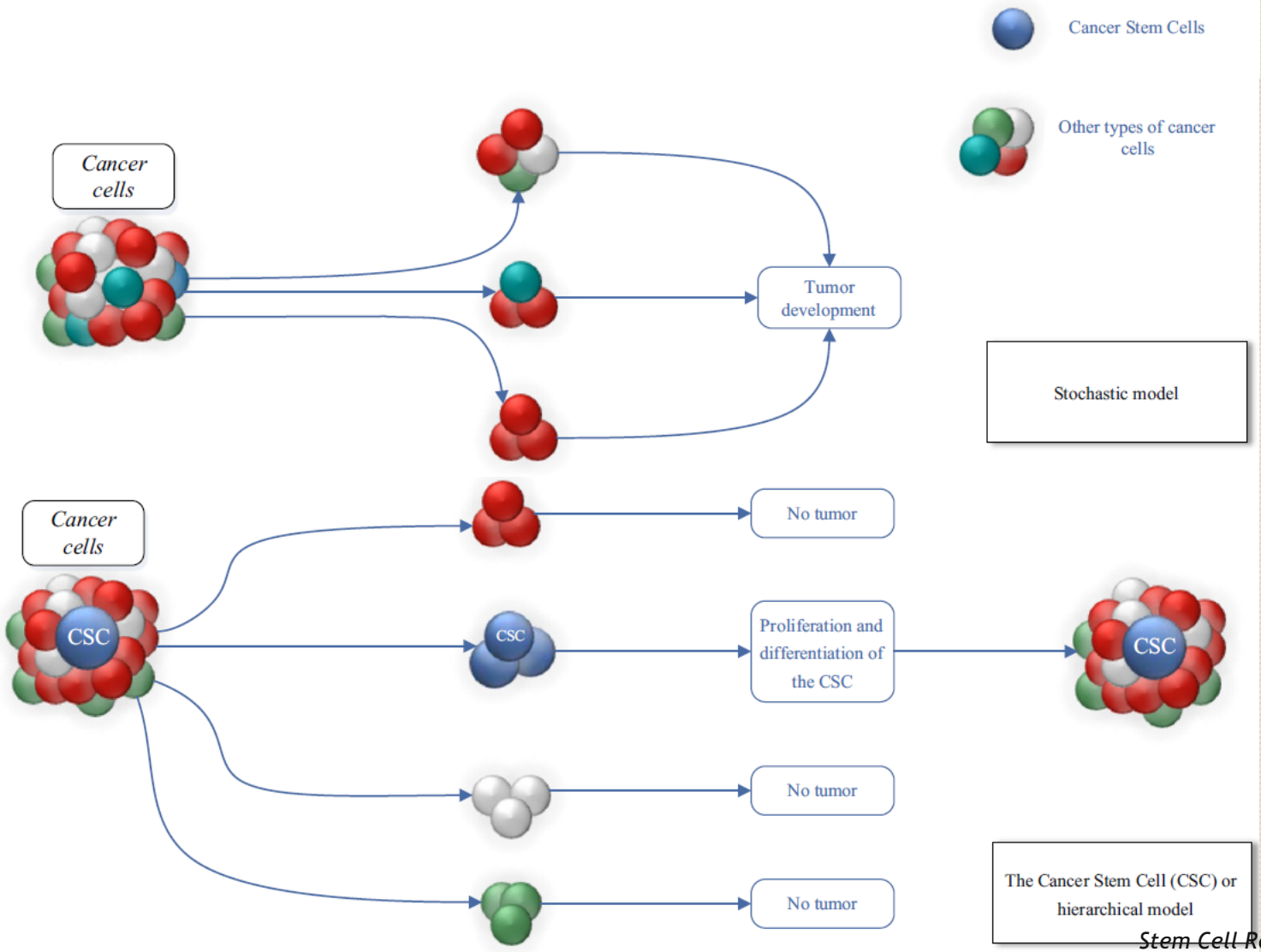


Bioessays **2009**, *31*, 1038–1049

Cancer Stem Cells

- Possess characteristics of both stem cells and cancer cells
  - Undergo asymmetric cell division generating daughter cells where one retains stem-like properties and one progresses through cell division and differentiation
- Make up small a portion of the overall tumor
  - Up to 20% of cells in some solid tumors have been identified as possible CSCs
- Still some debate about origin of cancer, are CSCs real?
- More evidence mounting in favor of CSCs: including the heterogeneity that is characteristic of many tumor types

Origins of Cancer- Hypotheses



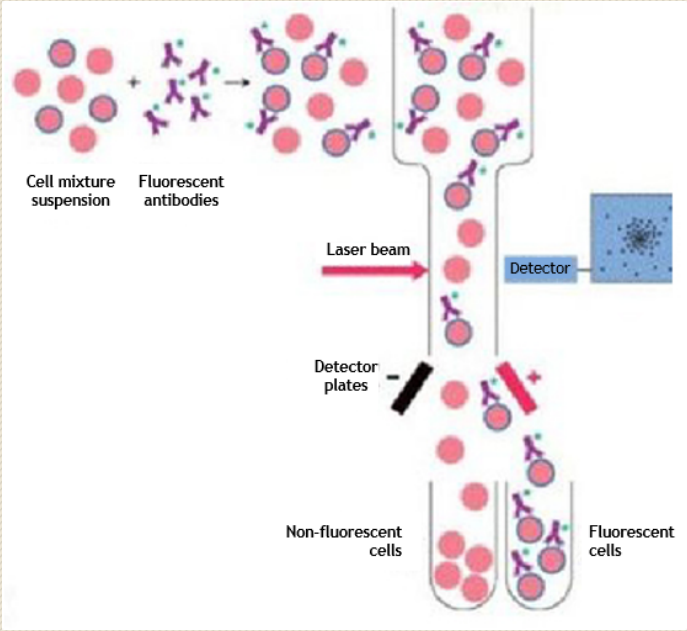
Stem Cell Rev. Rep. **2015**, *11*, 909-918

Cancer Stem Cells- Identification

- CSCs have been identified in various tumor types: AML, brain, breast, colon, liver, prostate, ovarian, pancreatic, bone, kidney, skin, and head and neck cancers
- Identified by markers that vary depending on the tumor type
  - Cell surface proteins
  - Cellular activity
- Not exact: not unique to CSCs (also in normal stem cells of the tissue)
- No single marker is known to easily identify CSCs

Tumor Type	Markers
Acute Myeloid Leukemia (AML)	$CD34^{+}CD38^{-}$
Brain Cancer	$CD133^{+}CD15^{+}$
Breast Cancer	$CD44^{+}CD24^{-/low}$ $CD133^{+}$ $ALDH\text{-}1^{+}$
Liver Cancer	$CD133^{+}$ $CD90^{+}CD45^{-}$ $CD44^{+}$ $CD24^{+}$
Prostate Cancer	$CD44^{+}\alpha2B1integrin^{high}CD133^{+}$
Pancreatic Cancer	$CD44^{+}CD24^{+}ESA^{+}$

Cancer Stem Cells- Identification



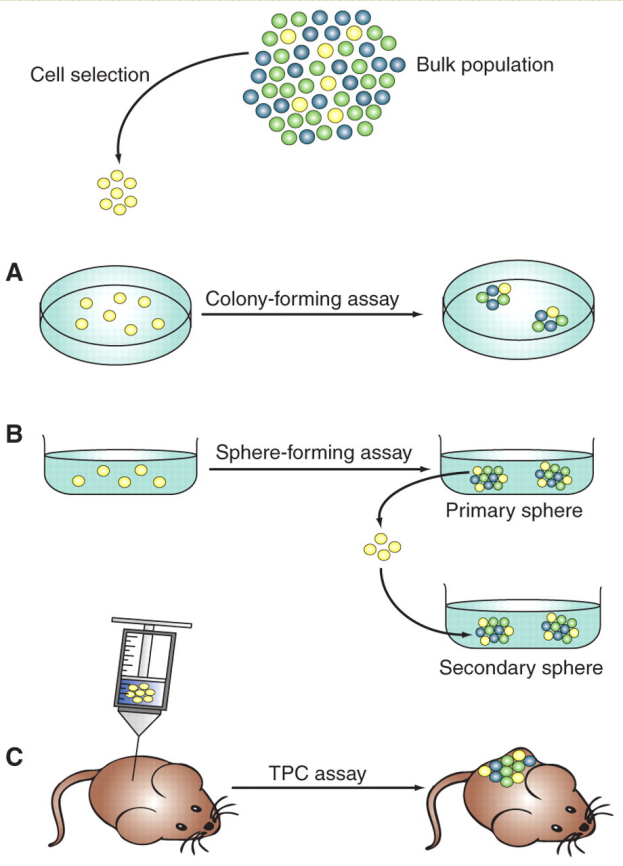
1. Patient samples have cell subpopulations sorted by flow cytometry based on markers present or not present
2. Cells baring the desired markers are transplanted into immunocompromised mice
3. Allow tumors to grow (if CSCs present)

OR

1. Patient samples are diluted down to low concentrations
2. Take aliquots and implant into immunocompromised mice
3. Allow tumors to grow (if CSCs present)

http://beweb.ucsd.edu/courses/senior-design/projects/2010/project_14/design-goals-alternatives.html

Cancer Stem Cells- Identification



1. Patient sample cells are sorted for desired markers
2. Plated at low density on a solid substrate
3. Allow colonies to grow (if progenitor or CSCs present)

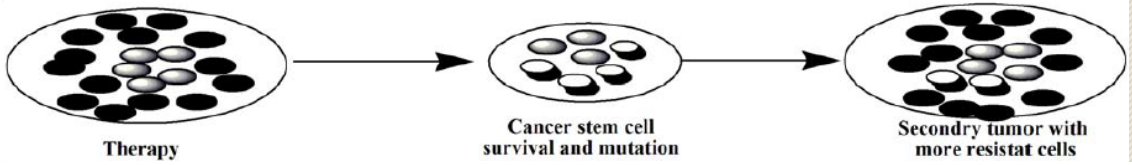
OR

1. Patient sample cells are sorted for desired markers
2. Suspended in a semi-liquid medium at low density
3. Allow spheres to grow (if CSCs present)

J. Cell Sci. **2010**, *123*, 2357-2368

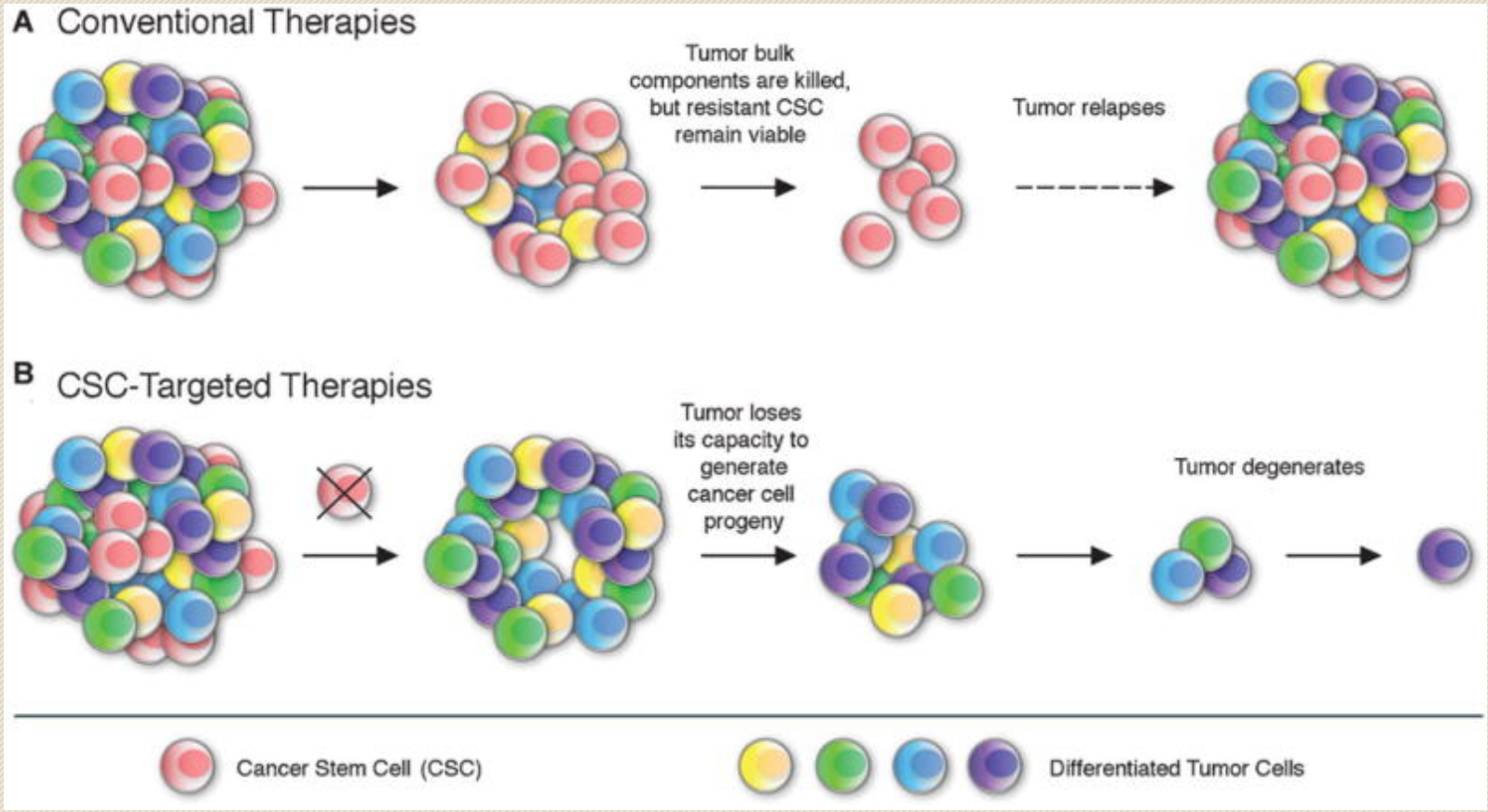
Cancer Stem Cells- The Problem

- Chemo- and radio-resistance
  - Chemo: Post-treatment $HER2^+$ breast cancer biopsy samples were enriched in $CD44^+CD24^{-/low}$ cells
    - Before: 4.7% vs after: 13.6%
    - Ability to form mammospheres before: 13.3% vs after: 53.5%
  - Radio: lower levels of ROS were detected in CSC enriched human breast cancer samples after radiation relative to non-CSC populations
    - Higher levels of expression of several ROS scavengers (superoxide dismutase 2, SOD2, methionine sulfoxide reductase A, MSRA) were found in CSC enriched samples
- Metastasis
  - $CD44^+$ breast CSCs from primary tumors and secondary lung metastases resulted in metastasis when transplanted into immunocompromised mice
- Recurrence



Mini-Rev. Med. Chem. **2014**, *14*, 20-34
J. Natl. Cancer Inst. **2008**, *100*, 672 – 679
Nature **2009**, *458*, 780-783
Proc. Natl. Acad. Sci. USA **2010**, *107*, 18115-18120

Cancer Stem Cells- The Problem



Bioessays **2009**, *31*, 1038–1049

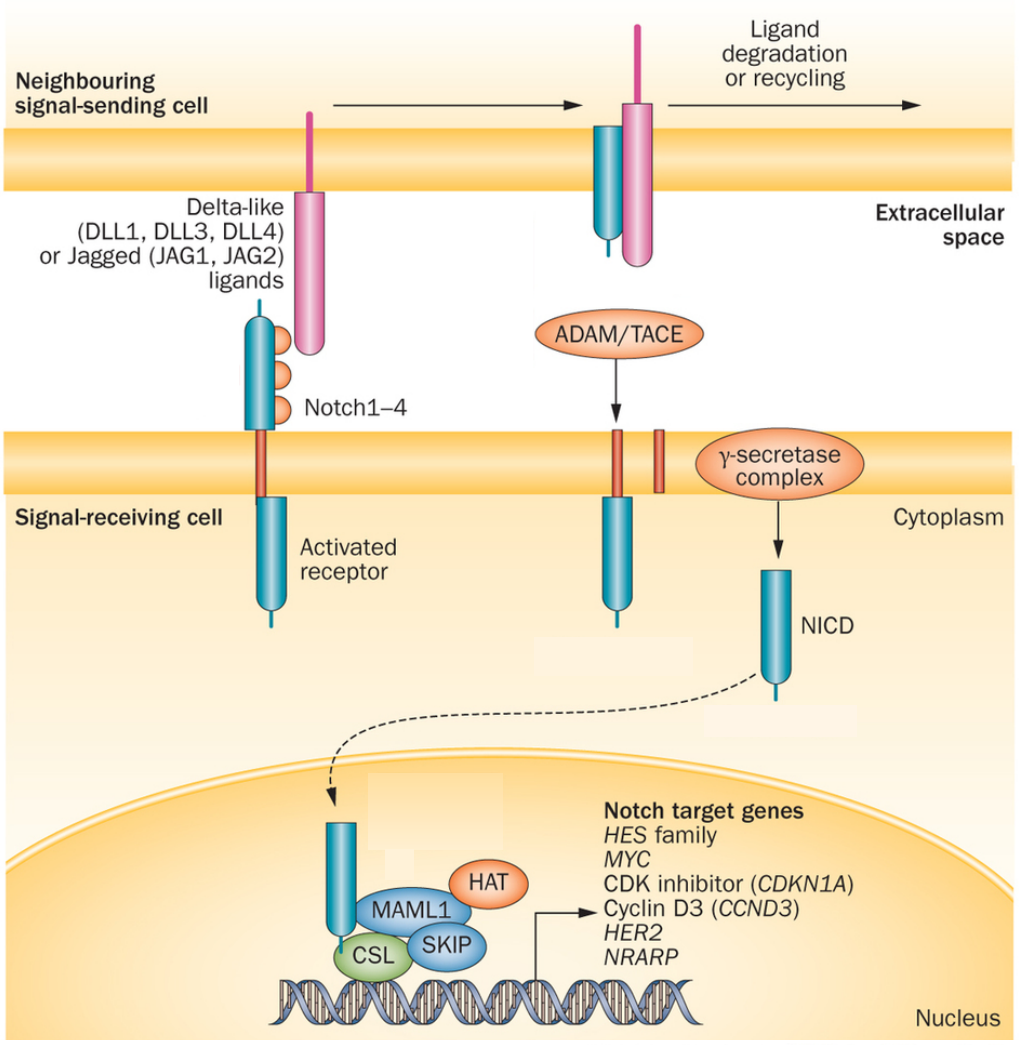
Cancer Stem Cells- Targeting

- Due to slow growth/replication rate, many standard chemotherapeutics won't work
- CSCs are heavily reliant on pathways that control self-renewal, embryonic development, and differentiation
  - Wnt
  - Hedgehog (HH)
  - Notch
  - Transforming Growth Factor ß (TGF-ß)
- Theoretically, inhibiting these pathways should target CSCs, selectively killing them
- Killing these "seed" cells should make tumors vulnerable to standard treatments

The Notch Pathway

- Originally discovered in *Drosophila melanogaster*
- Highly conserved embryonic developmental pathway
- Cell-to-cell contact is required for Notch signaling between cells
  - Ligands are presented on one cell and the receptor on the other
- 4 Notch receptors (Notch 1-4)
  - Single pass transmembrane cell surface receptors
  - Active receptors are heterodimers that originate from a single precursor which is cleaved then reconnected non-covalently
- 5 Notch ligands (Delta-like ligand [DLL] 1,3,4, Jagged [JAG] 1,2)
- Gene targets include HES and HEY transcriptional repressors, and NF-κB

The Notch Pathway



Nat. Rev. Clin. Oncol. **2015**, *12*, 445-464

The Notch Pathway- Role in Cancer

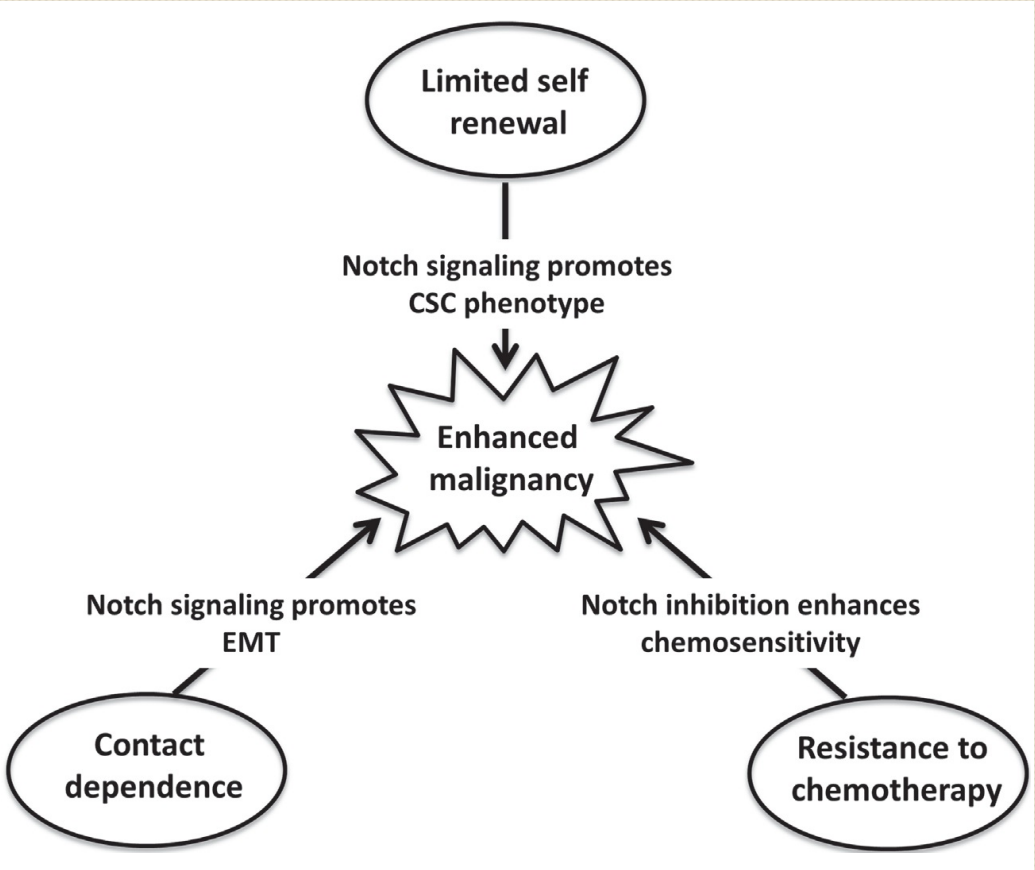
Breast Cancer

- Notch signaling activity in breast cancer is common, up to 50% of cells have Notch activation
- Notch 1 activation resulted in accelerated tumor growth *in vivo*
- High JAG 1 and Notch 1 expression levels are correlated with poor patient survival
- Reduction in Notch 1 and 4 activity lead to reduction in amount of $CD44^{+}/CD24^{low}$ cells
  - Also reduced tumorigenicity after transplantation into immunocompromised mice

Carcinogenesis **2013,** *34*, 1420–1430

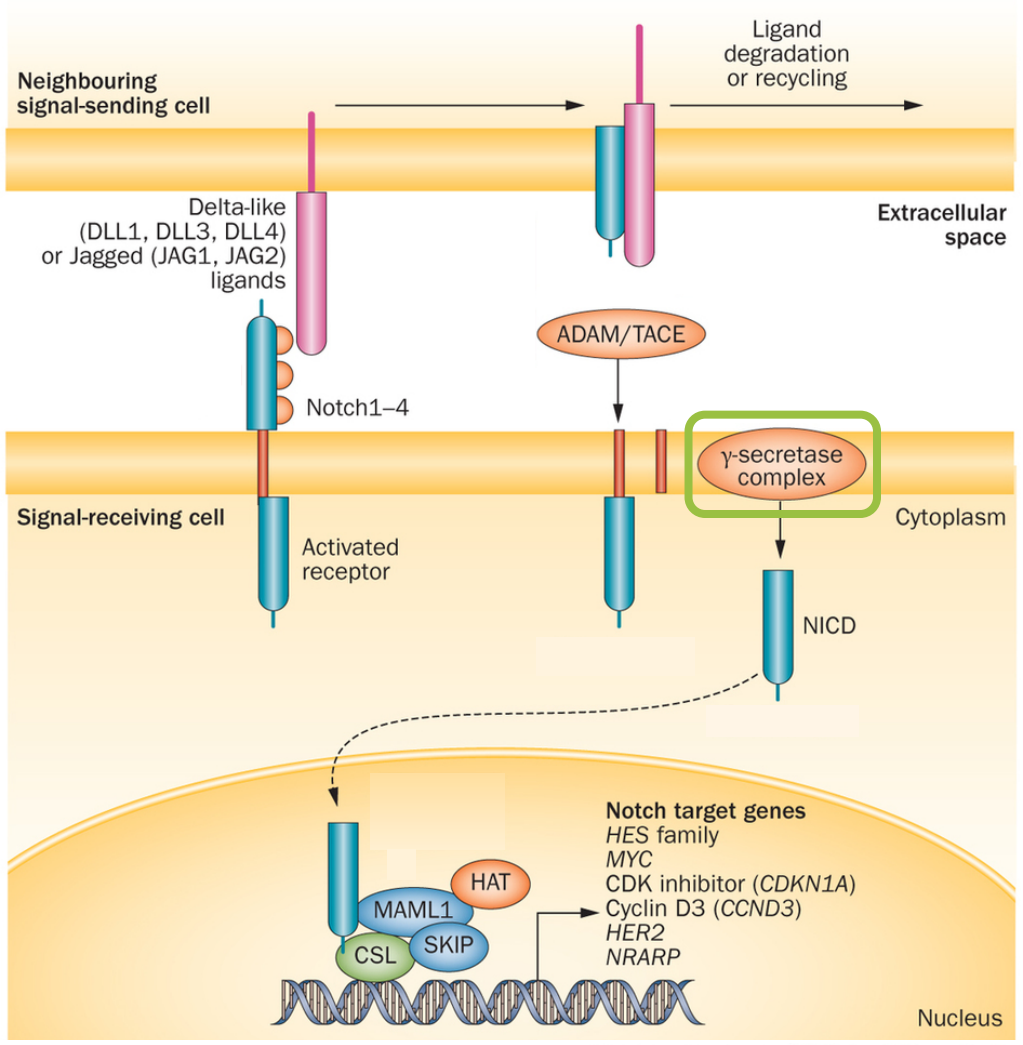
The Notch Pathway

- In most tissues, maintains an undifferentiated state
- In several tumor types, the expression level of Notch pathway components positively correlated with tumor grade
- Aids in CSC survival
- Plays a role in Epithelial-Mesenchymal Transition (EMT)
- Contributes to chemoresistance



Carcinogenesis **2013**, *34*, 1420-1430

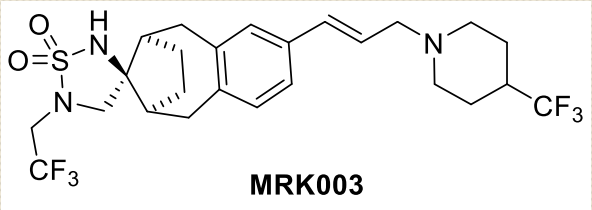
The Notch Pathway- Targets



Nat. Rev. Clin. Oncol. **2015**, *12*, 445-464

Targeting Agents- Merck

- MRK-003
  - The preclinical/nonhuman compound used to guide the development of another Merck GSI, MK-0752



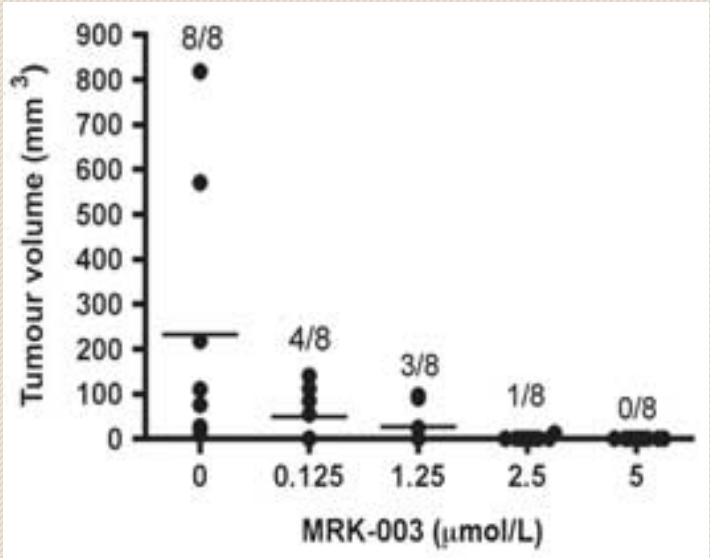
MRK003

  - Originally tested against Alzheimer's disease for its ability to block AB40 accumulation
    - Subnanomolar activity against γ-secretase (0.24 nM)
    - *in vivo* efficacy against AB40 accumulation
  - Orally bioavailable

Bioorg. Med. Chem. Lett. **2005**, *15*, 4212-4216

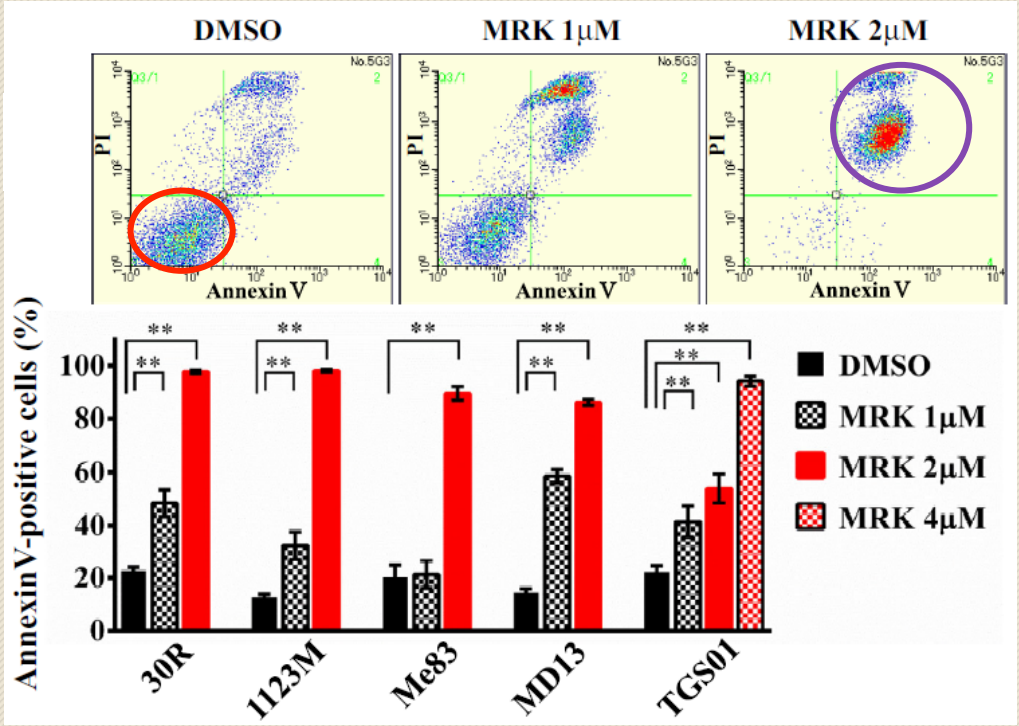
Targeting Agents- MRK-003

- Kondratyev *et al*. treated primary tumor cells with either DMSO or MRK-003 for 4 days
- Injected cells from the spheres that formed into mice subcutaneously and allowed tumors to grow
- All animals were sacrificed when a tumor that was 10% of the weight of any occurred



Targeting Agents- MRK-003

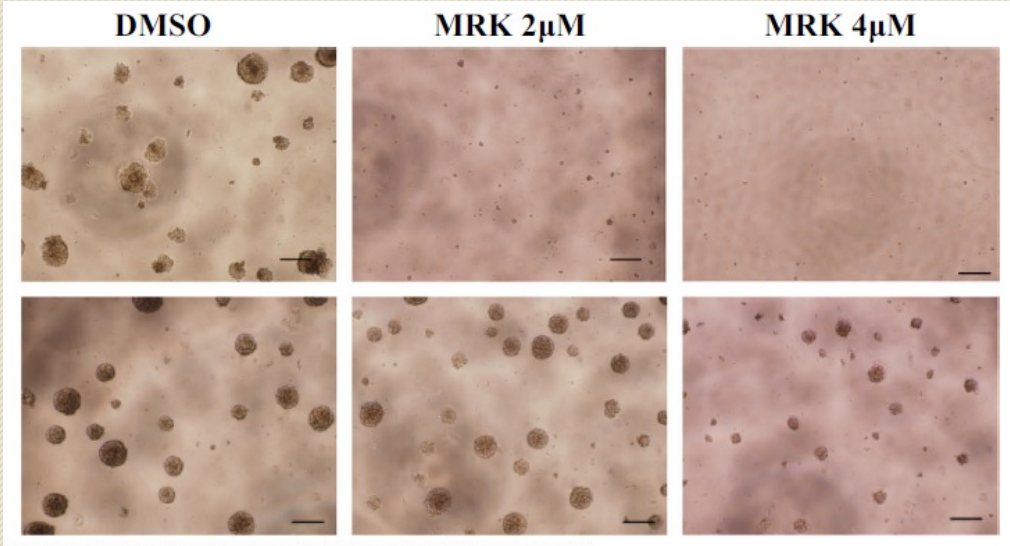
- Tanaka *et al*. treated cells derived from GBM patient sample neurospheres with MRK-003
- MRK-003 induced apoptosis more vs DMSO control
- Lower left quad (red circle) = viable cells
- Upper right quad (purple circle) = apoptoic cells



J. Neurooncol. **2015**, *121*, 239-250

Targeting Agents- MRK-003

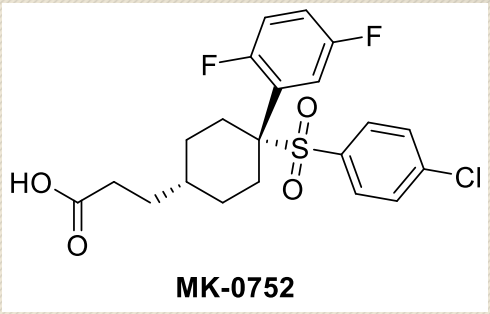
- Tanaka *et al*. treated patient derived samples with DMSO or MRK-003 for 7 days
- MRK-003 resulted in significantly decreased tumorosphere formation relative to DMSO control
- Upper panel is from MRK "relatively sensitive" tumor
- Lower panel is from MRK "relatively resistant" tumor



J. Neurooncol. **2015**, *121*, 239-250

Targeting Agents– Merck

- MK-0752



MK-0752

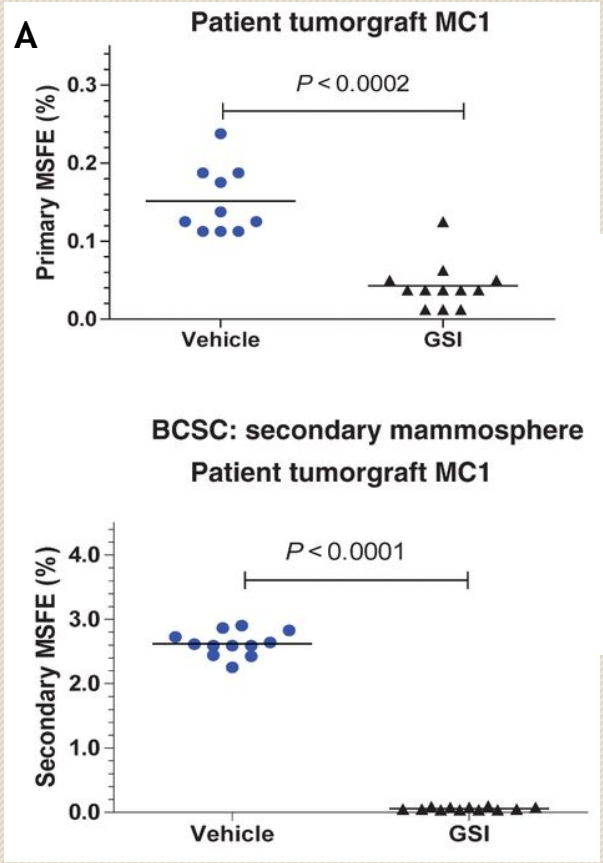
  - Originally tested against Alzheimer's disease for its ability to block Aß40 accumulation
    - IC_{50} = 5 nM
    - *in vivo* efficacy against Aß40 accumulation
  - Orally bioavailable
- Has been in 9 clinical trials mostly Phase I, but also Phase I/II
  - Either as a single agent or in combination

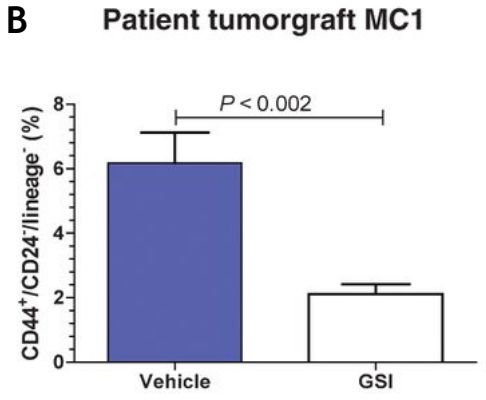
Targeting Agents– MK-0752

- Schott *et al*. transplanted patient derived metastatic breast cancer cells into immunodeficient mice
- Treated with either vehicle or MK-0752 (100 mg/kg po) for 3 days

A. Cells were harvested and allowed to grow mammospheres
   - Significantly reduced mammosphere formation in both primary and secondary assays relative to vehicle control

B. Cells were assessed for CSC markers ($CD44^+/CD24^-$)

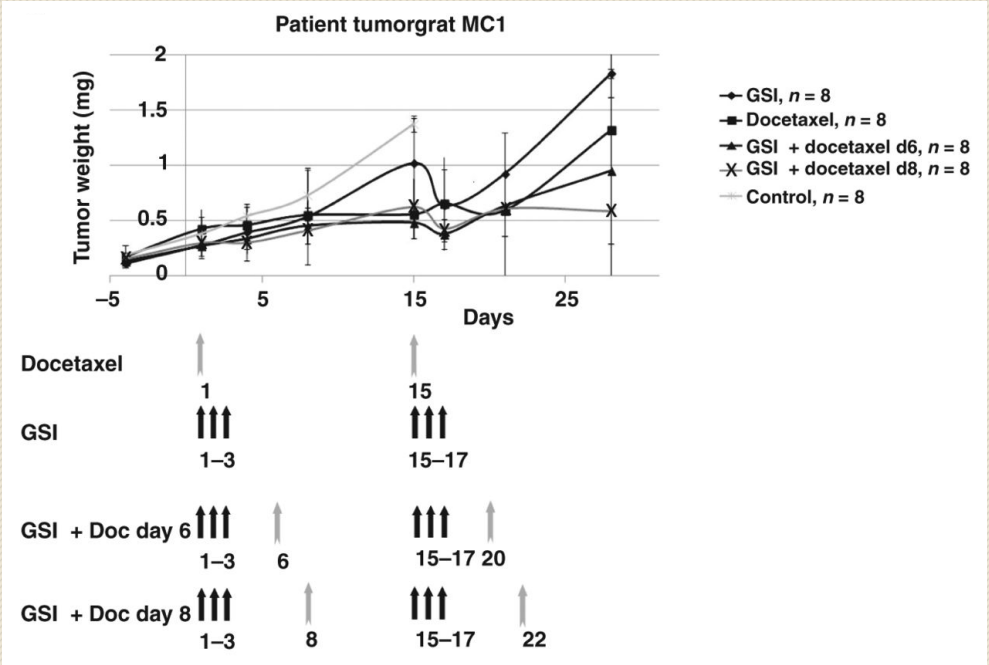




Clin. Cancer Res. **2013**, *19*, 1512-1524

Targeting Agents– MK-0752

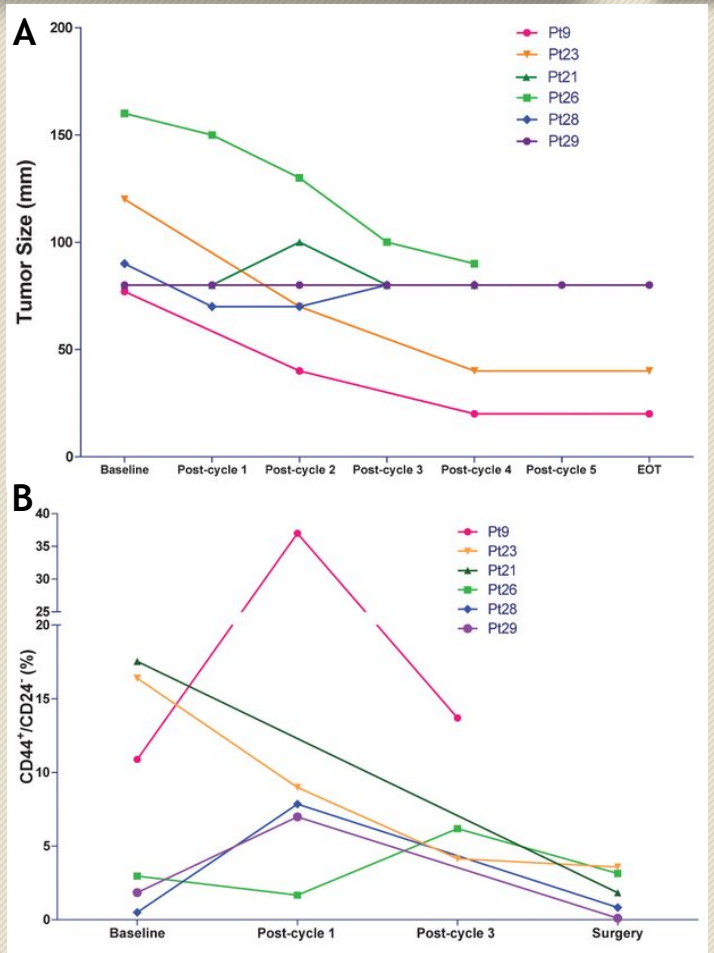
- Schott *et al*. transplanted patient derived metastatic breast cancer cells into immunocompromised mice
- Treated with either vehicle, MK-0752 (100 mg/kg), docetaxel (10 mg/kg), or both
  - Clinically relevant dosing schedule shown
- Significant difference between MK-0752 treatment and vehicle
- Significant difference between docetaxel alone and combination treatments



Clin. Cancer Res. **2013**, *19*, 1512-1524

Targeting Agents– Clinical Trials MK-0752

- 5 Completed clinical trials
  - For patients with advanced cancers
  - In combination with Gemcitabine, Ridaforolimus, or Docetaxel
  - Well tolerated in pediatric patients
- 3 Terminated clinical trials
  - Mainly due to toxicity and lack of efficacy
- 1 Active clinical trial for the treatment of early stage breast cancer in combination with Tamoxifen Or Letrozole

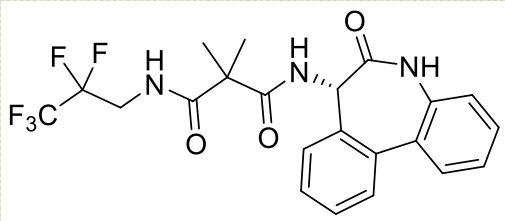


ClinicalTrials.gov

Clin. Cancer Res. **2013**, *19*, 1512-1524
Brit. J. Cancer **2014**, *111*, 1932-1944

Targeting Agents- Clinical Trials Roche

- RO4929097



RO4929097

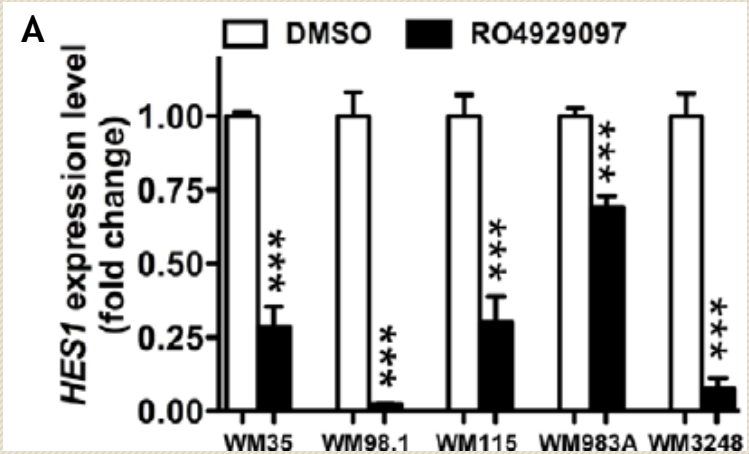
  - Investigated in both Alzheimer's disease and cancer
    - γ-Secretase IC_{50} = 4 nM
    - More selective inhibition for Notch cleavage over Aβ40
  - Selective (>100 fold selectivity over 75 tested proteins)
  - Orally bioavailable
- Has been in 35 clinical trials, both Phase I and Phase II
  - Either as a single agent or in combination
- No longer in development by Roche

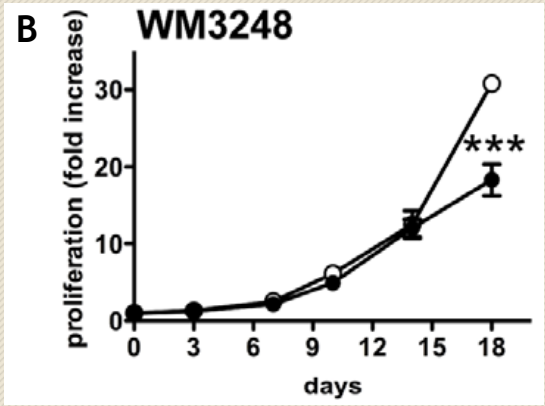
Targeting Agents– RO4929097

- Huynh *et al*. treated aggressive melanoma cancers with either DMSO or RO4929097 (10μM)

A. mRNA levels were determined for the downstream target gene of HES1 in treated and untreated cells
   - RO4929097 inhibits the Notch pathway *in vitro*

B. Treatment with RO4929097 resulted in significantly reduced cellular proliferation





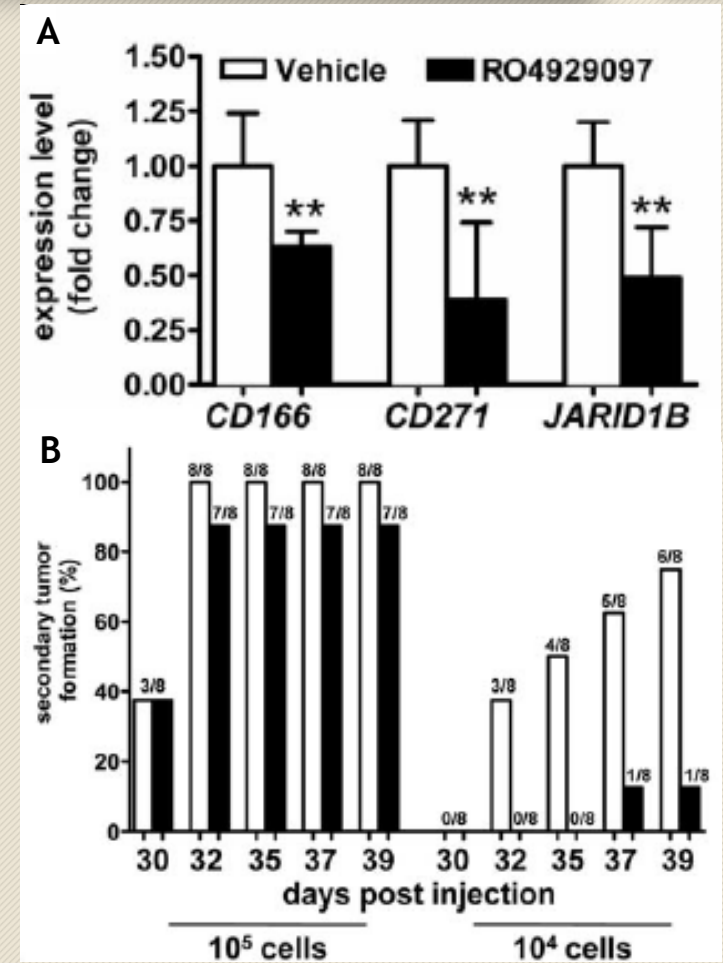
PLoS ONE **2011**, *6*, 1-10

Targeting Agents– RO4929097

- Huynh *et al*. transplanted WM3248 melanoma cells into immunocompromised mice

A. The expression levels of melanoma CSC markers were determined

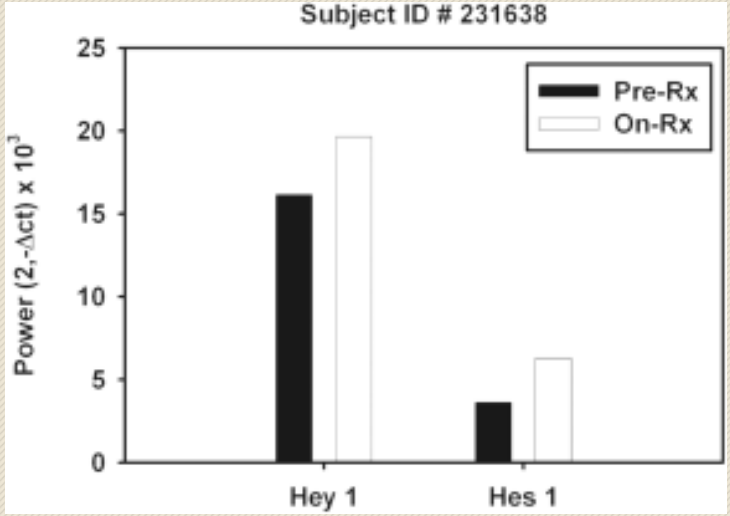
B. Primary tumor cells were collected from vehicle and RO4929097 treated mice and transplanted into new mice
   - Secondary tumors were untreated with additional compound



PLoS ONE **2011**, *6*, 1-10

Targeting Agents– Clinical Trials RO4929097

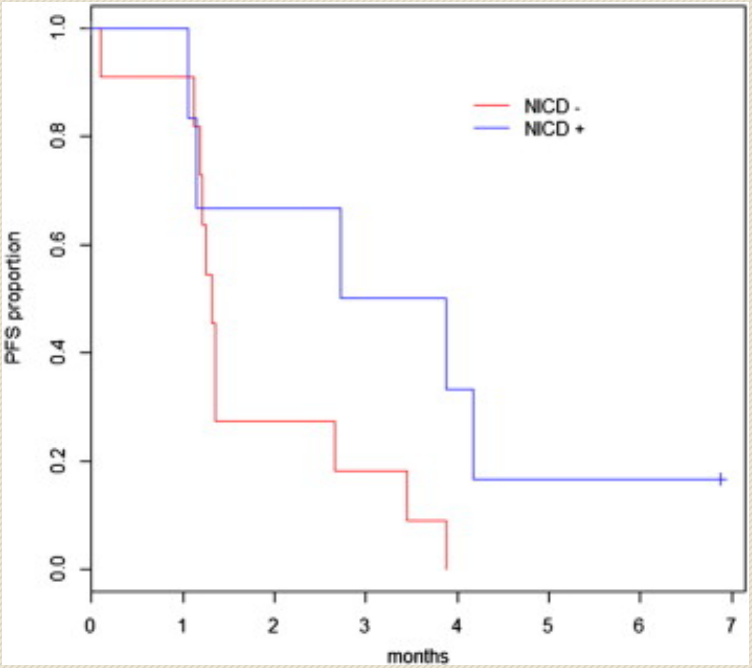
- Lee *et al.*, in a Phase II trial in metastatic melanomas, found that:
  - RO4929097 was well tolerated
  - 1 Partial response lasting 7 months
  - 8 patients had stable disease lasting at least through week 12
    - 1 continued for 31 months.
  - The 6-month progression-free survival rate was 9%
  - The 1-year overall survival rate was 50%
  - Lack of inhibition of Notch target genes



Cancer 2015, *121*, 432-440

Targeting Agents– Clinical Trials RO4929097

- Diaz-Padilla *et al.*, in platinum resistant ovarian cancers, found:
  - Also found RO4929097 to be well tolerated
  - 33% of patients reached stable disease (median duration = 3.1 months)
  - Median progression free survival (PFS) of study was 1.3 months (1.2–2.5)
  - Median PFS was higher when Notch intracellular domain detection was high (3.3 months vs 1.3 months for low NICD)



Gynecol. Oncol. **2015**, *137*, 216-222

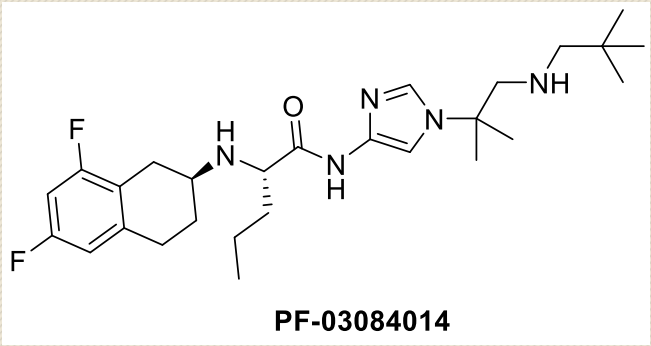
Targeting Agents– Clinical Trials RO4929097

- 15 Completed clinical trials
  - Typically for patients with advanced, metastatic, recurrent, or difficult to treat tumors
  - In various combinations including with other chemotherapeutic agents, radiotherapy, or surgery
- 13 Terminated clinical trials
  - Mainly due to too few subjects and discontinuation of RO4020097
- 4 Withdrawn clinical trials before recruitment occurred
- 3 Active clinical trials
  - For glioblastoma, breast cancer, and melanoma

ClinicalTrials.gov

Targeting Agents– Clinical Trials Pfizer

- PF-03084014



PF-03084014

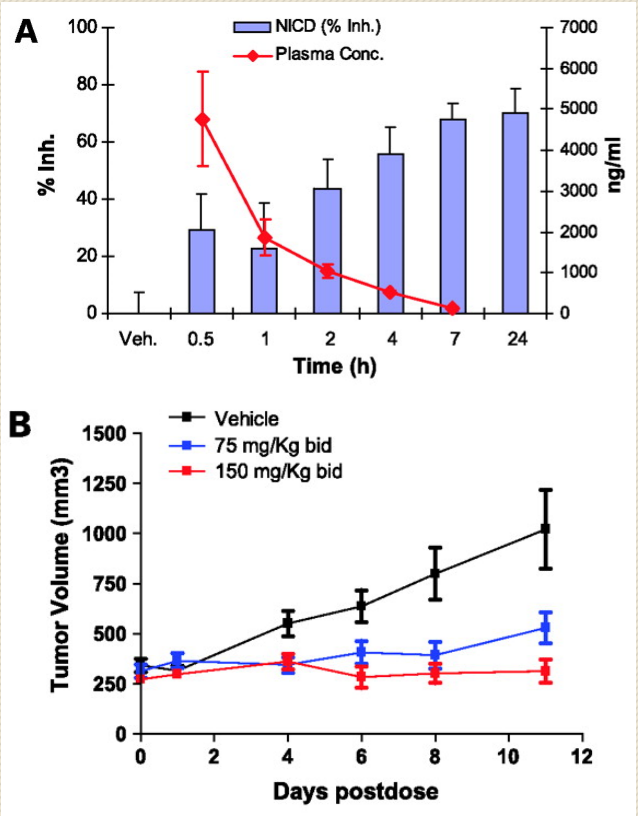
  - Originally tested against Alzheimer's disease for its ability to block Aβ40 accumulation
    - Good cellular activity against γ-secretase (1.2 nM)
    - *in vivo* efficacy against Aβ40 accumulation
  - 13.3 nM activity against Notch cleavage
  - Selective for γ-secretase
  - Orally bioavailable

Targeting Agents– PF-03084014

- Wei *et al*. transplanted leukemia cells into immunocompromised mice

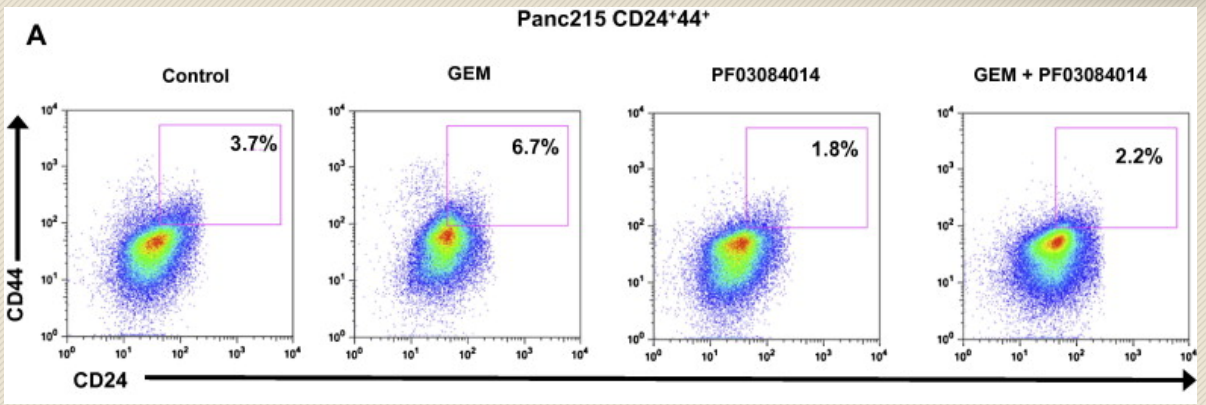
A. PF-03084014 treatment (50 mg/kg) resulted in significantly decreased levels of free NICD

B. PF-03084014 treatment resulted in reduced tumor volume
   - 92% reduction with 150 mg/kg dosing



Mol. Cancer Ther. **2010**, *9*, 1618-1628

Targeting Agents– PF-03084014

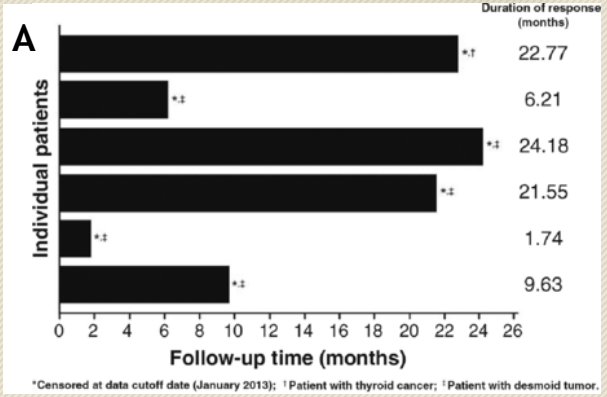


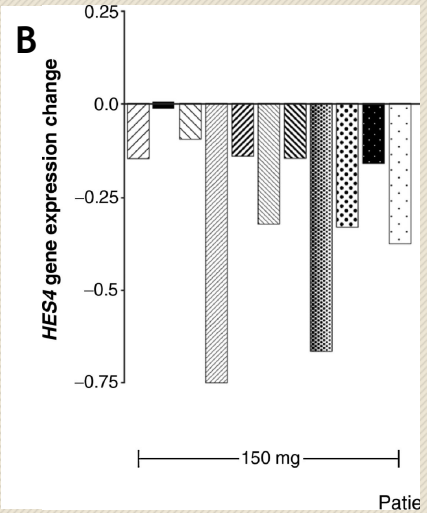
- Yabuuchi *et al*. transplanted pancreatic cancer cells into immunocompromised mice
  - In their 7 patient samples the percent CSCs varied greatly: 0.64 - 16.6%
- Treated with gemcitabine (25 mg/kg) or PF-03084014 (150 mg/kg) or both
  - Gemcitabine alone increased amount of $CD44^+/CD24^+$ cells
  - PF-03084014 alone decreased amount by 3.7%
  - Combination decreased amount by 3%

Cancer Lett. **2013**, *335*, 41-51

Targeting Agents– Clinical Trials PF-03084014

- 3 Withdrawn clinical trials
- 4 Terminated clinical trials
  - All terminated June 24, 2015 due to "change in strategy of development"
  - "There were no safety/efficacy concerns"
- 1 Active clinical trial
  - Phase II
  - Single agent, for desmoid tumors



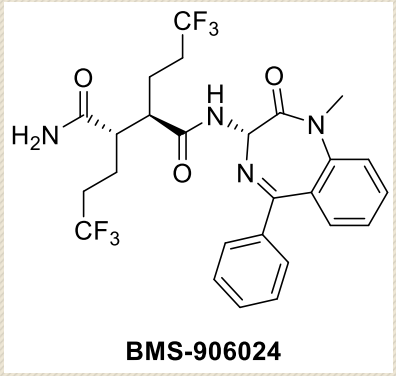


ClinicalTrials.gov

Clin. Cancer Res. **2015**, *21*, 60-67

Targeting Agents– Clinical Trials Bristol-Myers Squibb

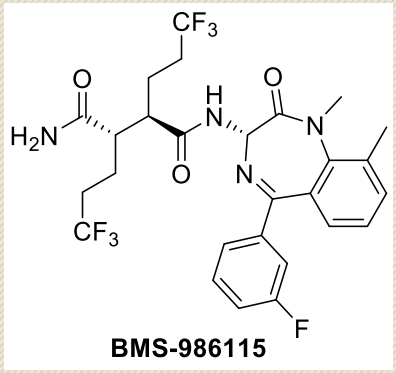
- BMS-906024



BMS-906024

- Selective
- IC_{50} = 2-3 nM
- Cellular IC_{50} (TALL-1) = 4 nM
- *in vivo* ED_{50} < 0.5 mg/kg in TALL-1

- BMS-986115



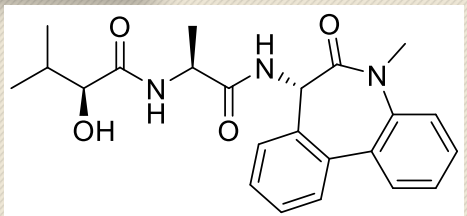
BMS-986115

- Orally bioavailable

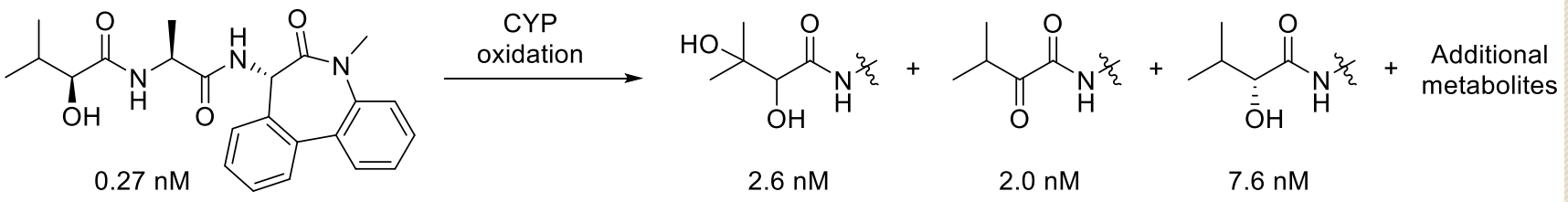
- Both in Phase 1 trials: Currently recruiting

ACS Med. Chem. Lett., **2015**, *6*, 523-527
Nat. Rev. Clin. Oncol. **2015**, *12*, 445-464
ClinicalTrials.gov

Targeting Agents– Clinical Trials Eli Lilly



- LY900009
- IC_{50} = 0.27 nM
- Solubility = 0.06 mg/mL (@ pH 2, 6, and 7.4)
- Metabolically labile
  - Especially the aliphatic tail
  - CYP3A4 primarily responsible for metabolism

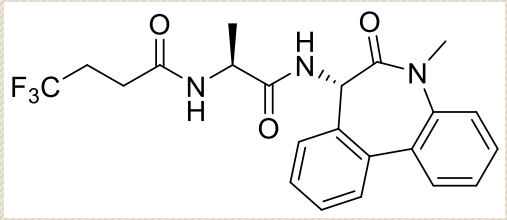


  - Need to improve metabolic stability, remove active metabolites, maintain potency
- 1 completed clinical trial – data not disclosed

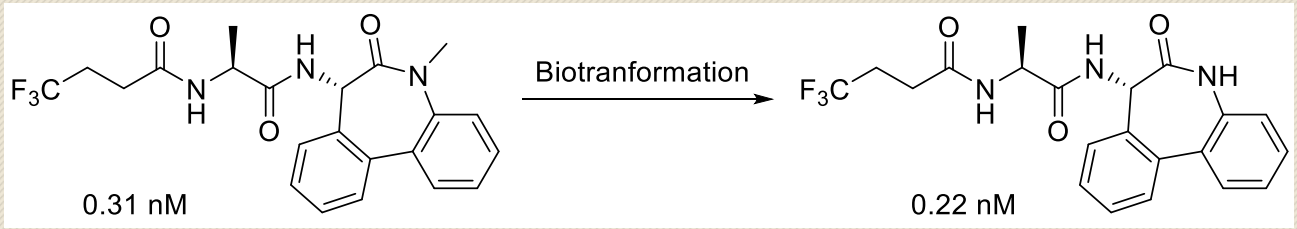
Porter, W. J., Discovery of a Novel Notch Inhibitor. Presented at the 8th SCI-RSC Symposium on Proteinase Inhibitor Design, Basel, Switzerland 2013

Targeting Agents– Clinical Trials Eli Lilly

- 2nd Generation compound



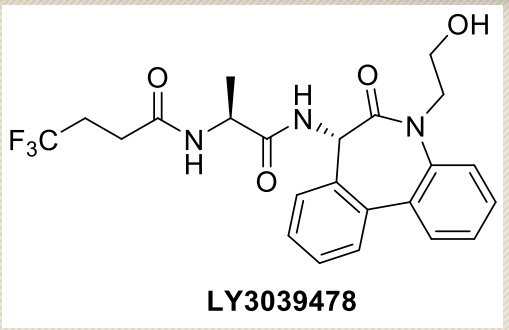
- IC_{50} = 0.31 nM
- Solubility = 0.20 @ pH 2.0, 0.22 @ pH 6.0, 0.02 mg/mL @ pH 7.4
- Metabolism significantly reduced
  - Major metabolism still by CYP3A4
  - Major metabolite N-dealkylation – more active than parent



Porter, W. J., Discovery of a Novel Notch Inhibitor. Presented at the 8th SCI-RSC Symposium on Proteinase Inhibitor Design, Basel, Switzerland 2013

Targeting Agents– Clinical Trials Eli Lilly

- LY3039478

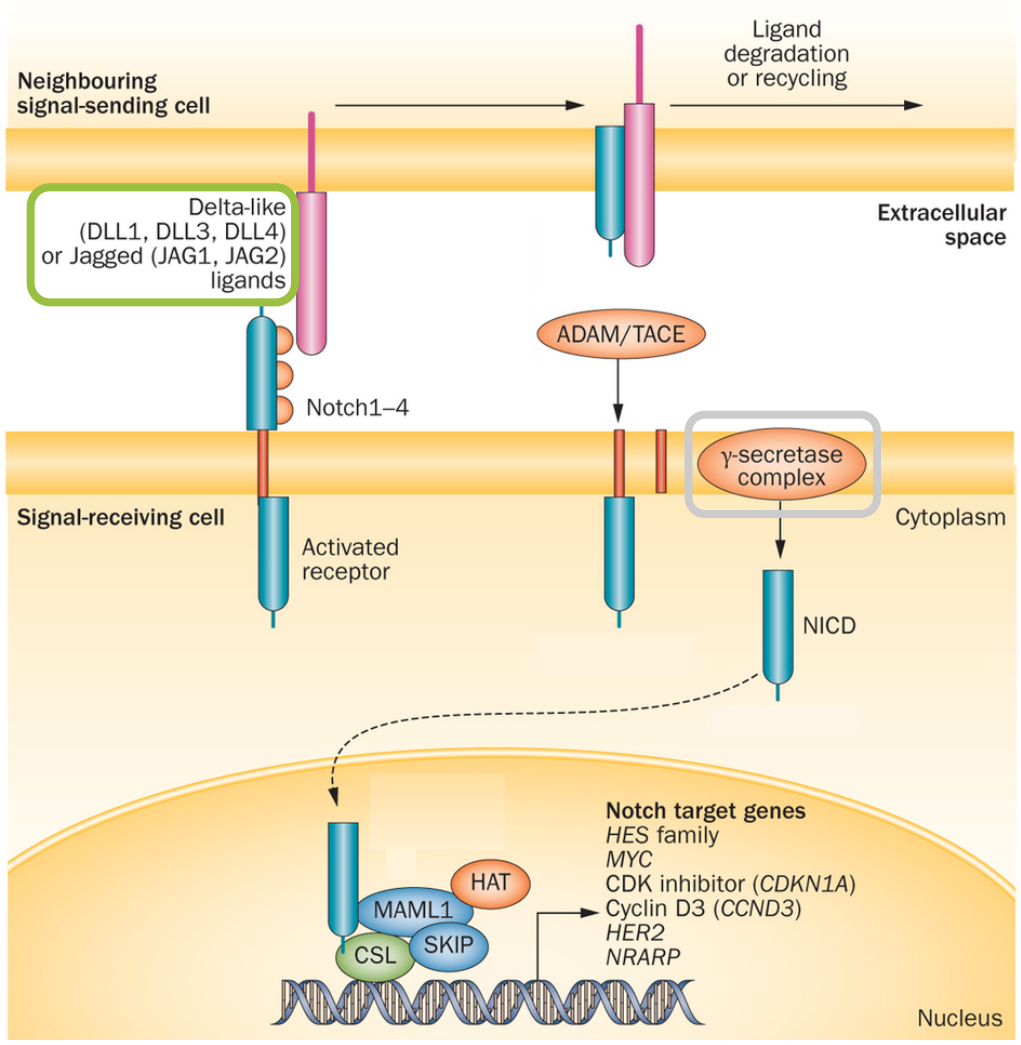


LY3039478

- IC_{50} = 0.41 nM
- Solubility = 0.89 @ pH 2.0, 0.88 @ pH 6.0, 0.88 mg/mL @ pH 7.4
- Metabolism significantly reduced
- No active metabolism identified in metabolism screen
- Good to moderate clearance (species dependent)
- Bioavailability: mouse, rat, dog; 65-67%
- In Phase I clinical trial
  - No preclinical data disclosed

Porter, W. J., Discovery of a Novel Notch Inhibitor. Presented at the 8th SCI-RSC Symposium on Proteinase Inhibitor Design, Basel, Switzerland 2013

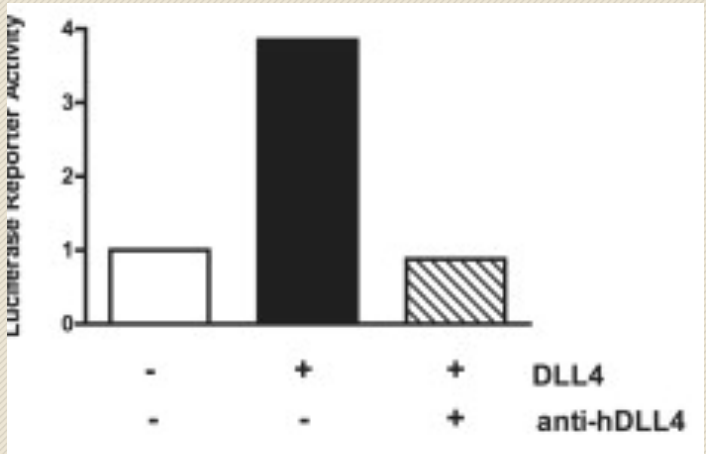
The Notch Pathway- Targets



Nat. Rev. Clin. Oncol. **2015**, *12*, 445-464

Targeting Agents– Clinical Trials Anti-DLL4

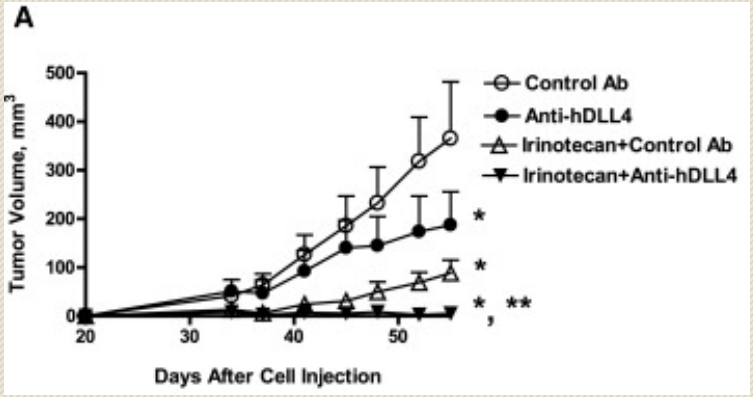
- It has been shown that inhibition of DLL4 results in non-productive angiogenesis
  - Leading to hypoxia at tumor and decreased tumor growth
- DLL4 inhibition has also been shown to be anti-tumorigenic via mechanisms other than angiogenesis
  - *in vitro* blockage of DLL4 via mAb resulted in reduction of Notch signaling

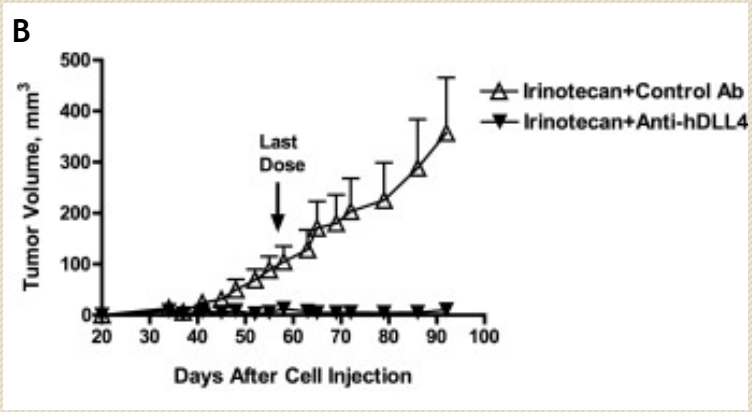


Cell Stem Cell **2009**, *5*, 168-177

Targeting Agents– Clinical Trials Anti-DLL4

- OMP-21M18
- Monoclonal antibody (mAb)
  - Selective for DLL4 over other Notch ligands
- Treatment of a colon tumor xenograph with OMP-21M18, irinotecan, or both resulted in reduced tumor volume compared to the control
- After stopping dosing tumors were allowed to continue growing (B)
  - Those treated with no OMP-21M18 continued to grow, OMP treated cells did not





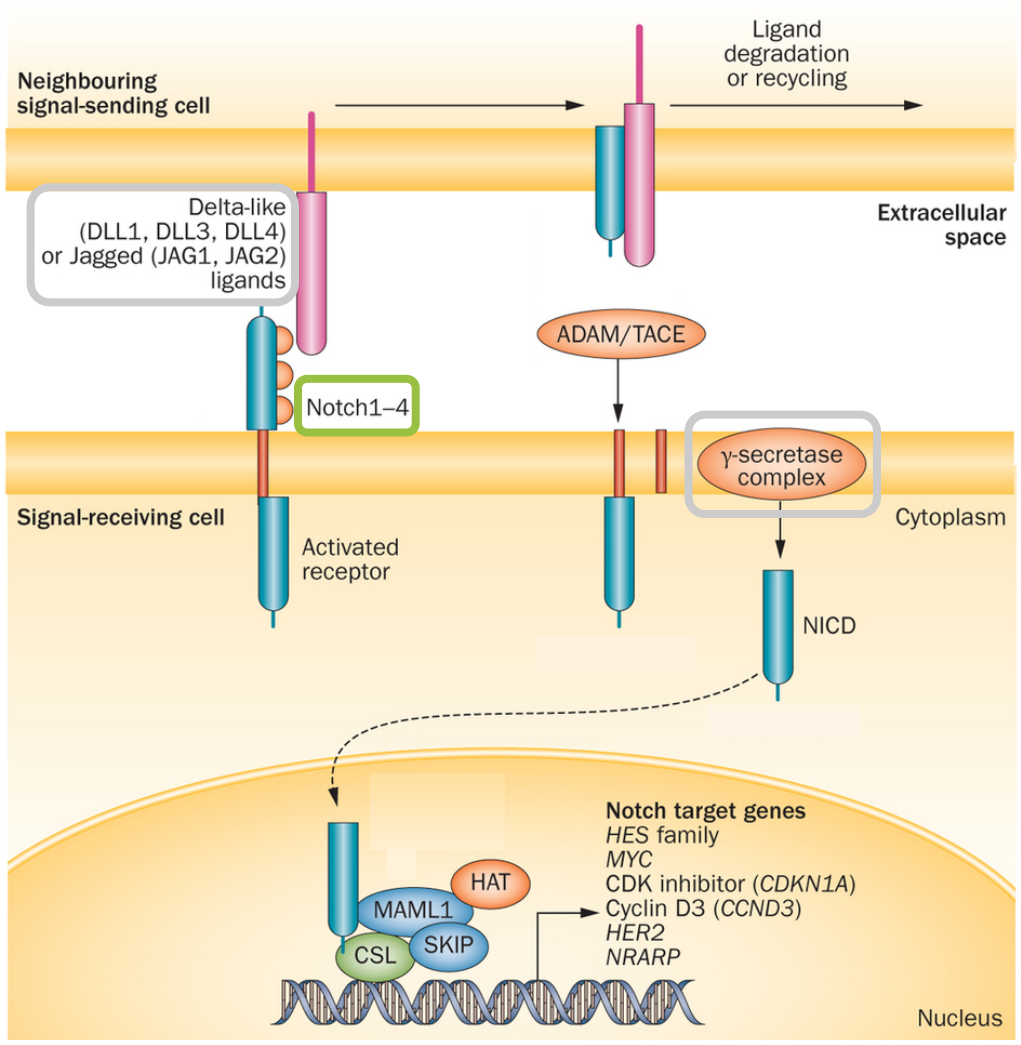
Cell Stem Cell **2009**, *5*, 168-177

Targeting Agents– Clinical Trials Anti-DLL4

- OMP-21M18
  - 1 Completed phase I clinical trial
  - 2 Active phase I clinical trials currently running
    - Single agent or in combination
    - For Non-small cell lung cancer and pancreatic cancers
  - 1 Currently recruiting clinical trial in combination with paclitaxel for the treatment of Pt resistant ovarian cancer
- MEDI0639
  - mAb, currently recruiting for phase I clinical trial for advanced solid tumors
- REGN421
  - mAb, completed phase I clinical trial for advanced solid tumors

Cell Stem Cell **2009**, *5*, 168-177

The Notch Pathway- Targets



Nat. Rev. Clin. Oncol. **2015**, *12*, 445-464

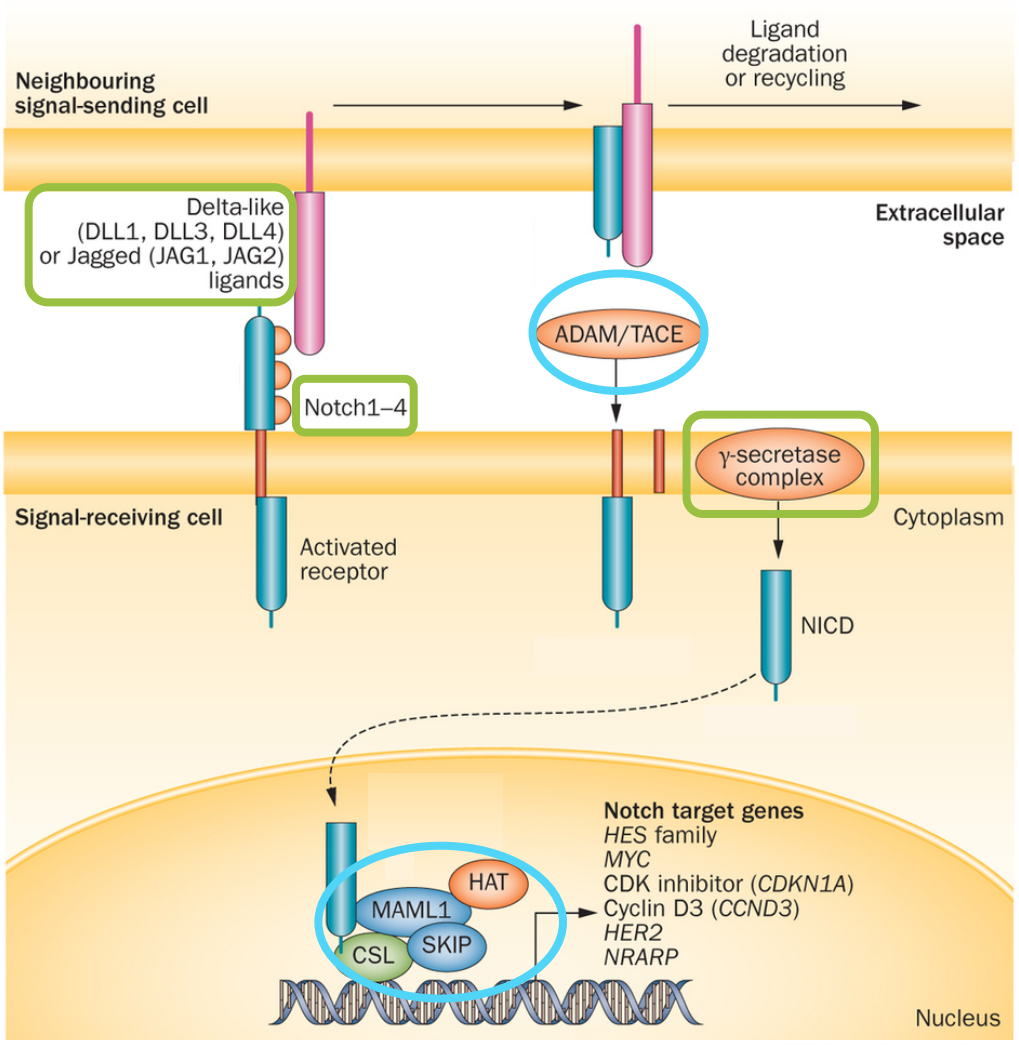
Targeting Agents– Clinical Trials Anti-Notch

- There are currently 2 anti-Notch antibodies in clinical trial
- OMP-52M51
  - Binds Notch 1
  - Selective over other Notch receptors
  - 2 Phase I clinical trials currently recruiting
- OMP-59R5
  - Binds Notch 2/3
  - Tested preclinically in a variety of tumor types with good efficacy
  - Tested in combination with chemotherapeutics with good efficacy
  - 1 Active phase I clinical trial
  - 2 Phase Ib/II clinical trials currently recruiting

Targeting Agents

- Notch pathway inhibitors alone are at best moderately effective
- Because they will in theory only kill CSCs, it would be ideal to combine these compounds/antibodies with another chemotherapeutic agent which results in non-CSC cell death
- Combinations of GSI+chemotherapeutic as well as antibody+chemotherapeutic have been/are being tested to varying degrees of success
- GSI treatment also can lead to toxicity
  - It was found co-treatment with a glucocorticoid could reverse this toxicity and does not hinder efficacy

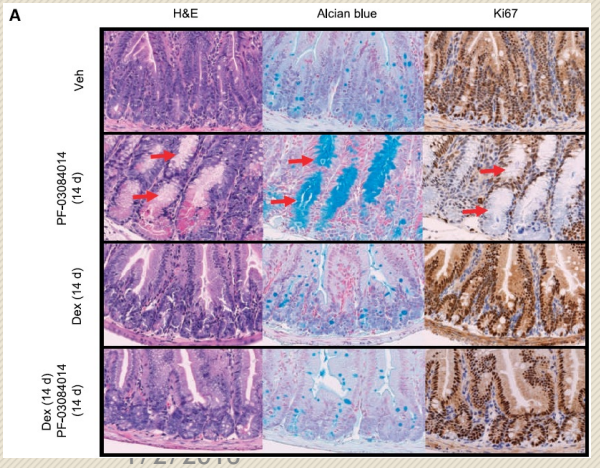
Potential Alternate Targets



Nat. Rev. Clin. Oncol. **2015**, *12*, 445-464

Current Challenges- Toxicity/ Efficacy

- Toxicity associated with Notch inhibition
  - One of the major reasons many GSIs do not make it past the preclinical/early clinical stages is due to dose limiting toxicity (DLT)
  - Most common DLT for GSIs is diarrhea and other gastrointestinal symptoms
    - Notch inhibition can cause differentiation of intestinal goblet cells and reduced absorption
    - Glucocorticoids can reverse this toxicity
- Efficacy at times looks poor in the clinic due to Notch targeting treatments being used in tumors with no CSCs, investigators need to screen



Mol. Cancer Ther. **2010**, *9*, 1618-1628

Current Challenges- Identification

- There is no universal CSC marker
  - Markers for each tumor type must be determined individually
  - Not all tumors of a given tissue express the same markers in different individuals
- There is no simple method of determining CSC content within a patient tumor
  - It can be unreliable to assess CSC presence via blood testing- not all markers are present in the blood
  - Identifying cell surface markers requires biopsies and then secondary typically indirect means to determine if CSCs are present
  - Or the assumption that the cell surface markers truly indicate CSCs
  - Assays to determine CSC presence tend to be based on secondary tumorigenicity
    - does not necessarily indicate CSCs, might be progenitor cells
- Difficult to assess any potential treatment without

What More Can Be Done?

- Alternative targets need to be explored:
- GSIs may not be the most efficient way to target CSCs
- Targeting protein-protein interactions should be considered
- Jagged 1 has also been implicated in CSC activation- consider it as a target
- Possibility for small molecule inhibition of Notch-ligand binding

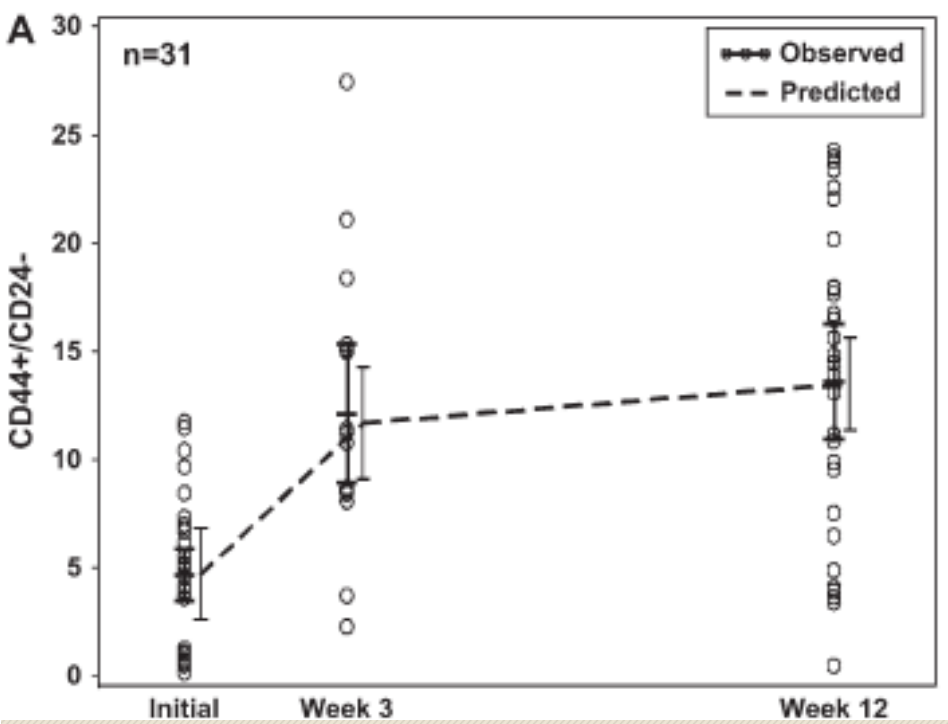
Conclusion

- CSCs have been identified in various tumor types by phenotypic and molecular means
  - CSCs contribute to chemo- and radio-resistance, metastasis, and recurrence
  - Targeting embryonic pathways essential to the survival of CSCs should be a viable means of killing them
- The Notch pathway has been implicated in the survival of CSCs
- By targeting γ-secretase there has been some success preclinically and clinically in targeting and killing CSCs, especially as part of combination therapies
- Targeting Notch and Notch ligands has also been explored via mAb and several clinical trials are underway to determine safety and dosing
- Determining a straightforward mean of identifying CSCs may be the key to targeting Notch in CSCs and moving drugs beyond the clinic

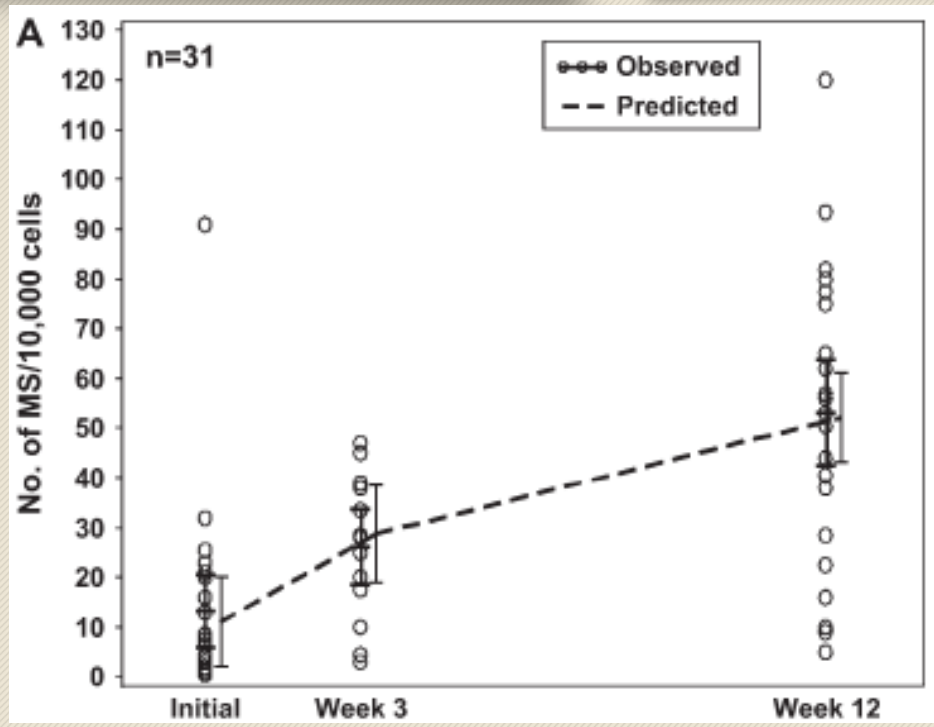
Acknowledgements

- Dr. Wipf
- Wipf group members past and present

Chemoresistance of CSCs



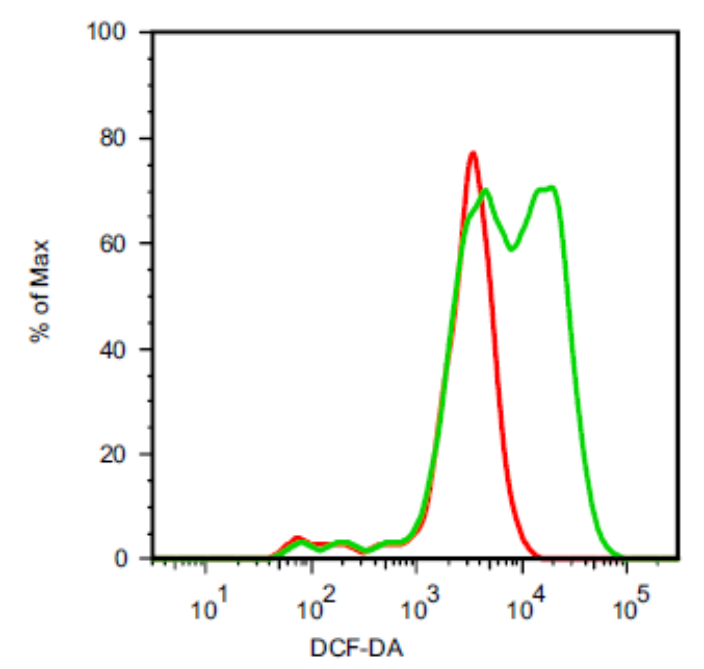
Effect of chemotherapy on the mean percentage of cells that express high levels of CD44 and low levels of CD24 (CD44+/CD24-/low) among HER2-negative patients. **Percentage of tumorigenic cells increased at week 3** (*P* < .001) **and remained high at surgery** (week 12) (*P* < .001).



Effect of chemotherapy on **mean mammosphere (MS) forming efficiency** before, during, and after treatment. All patients, *P* < .001.

J. Natl. Cancer Inst. **2008**, *100*, 672 – 679

Radioresistance of CSCs

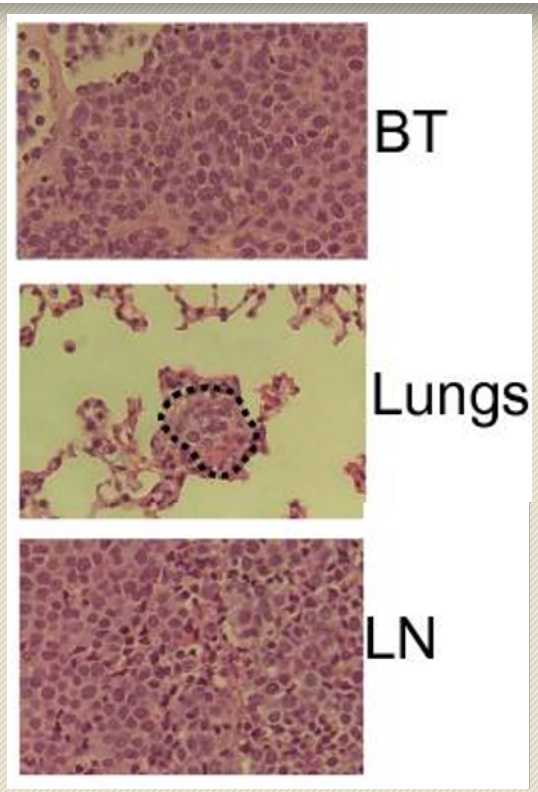


Human breast cancer from which $CD44^{+}CD24^{-/low}Lin^{-}$ cells (**cancer stem cell enriched population, red**) and "Not $CD44_{+}CD24^{-/low}$" Lin^{-} **non-tumorigenic cells, green**, were isolated using flow cytometry. Intracellular ROS concentrations were subsequently measured by DCF-DA staining for the two populations.

- **ROS levels were significantly lower in CSC enriched sample**

Nature **2009**, *458*, 780-783

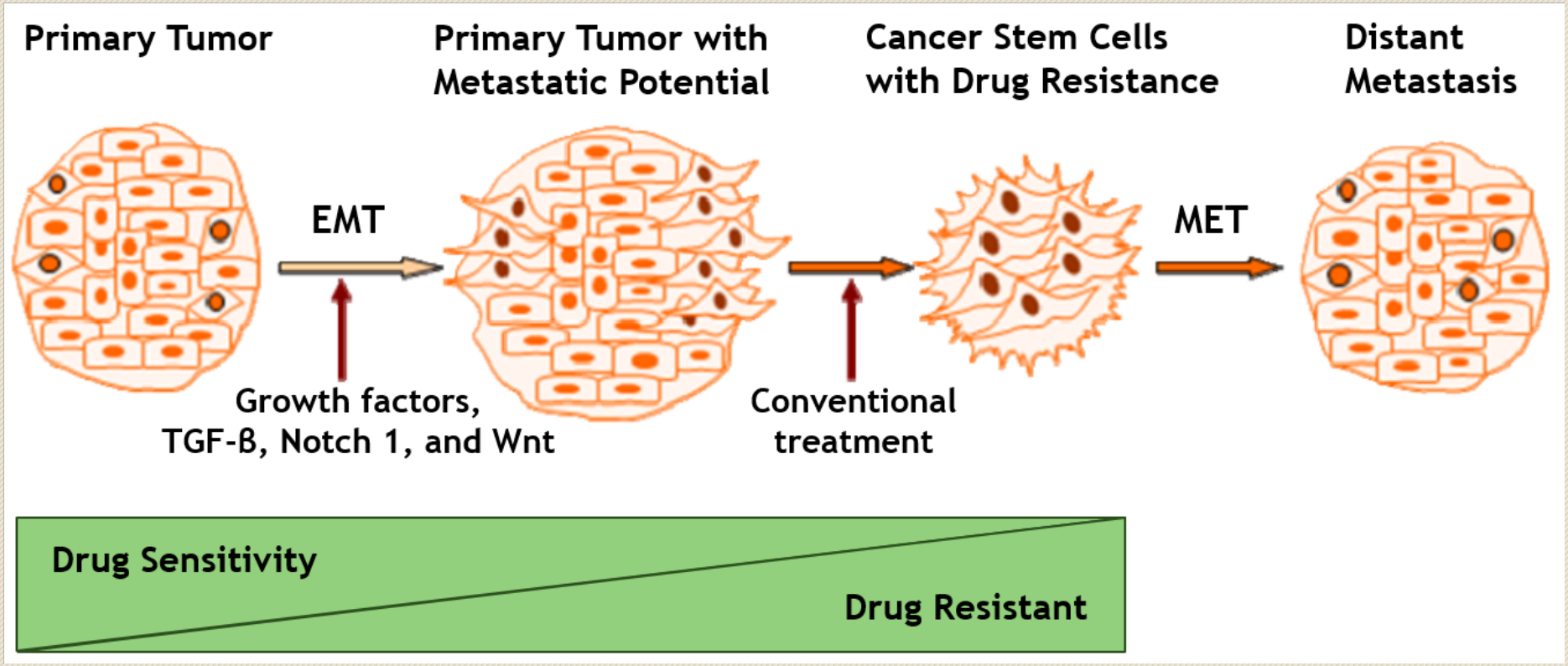
CSCs and Metastasis



Representative H&E stains of sections from the breast tumor (BT), dissected lungs, and lymph nodes (LN) from a NOD/ SCID mouse transplanted with $CD44^{+}$ human triple negative breast cancer tumor cells (Magnification: 200×)

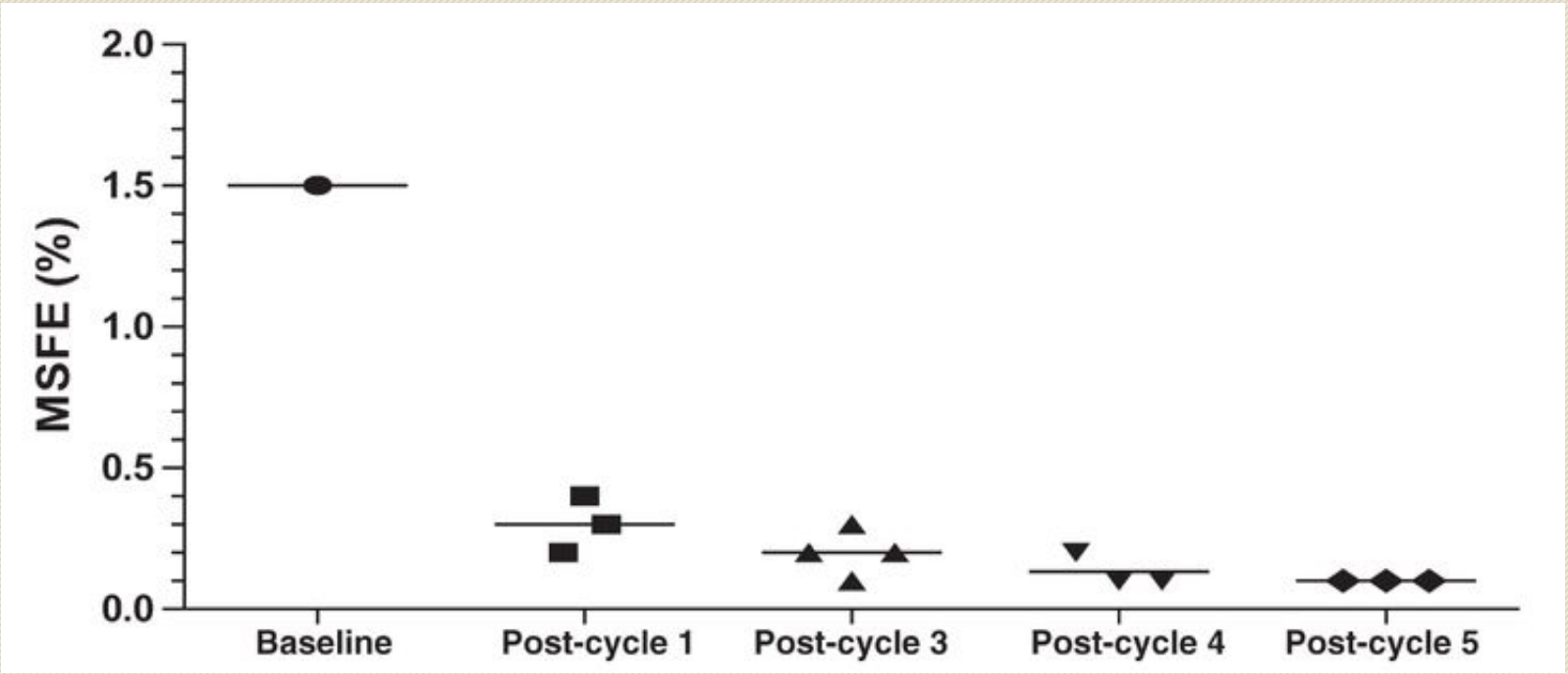
Proc. Natl. Acad. Sci. USA **2010**, *107*, 18115–18120

The problem with CSCs and Notch



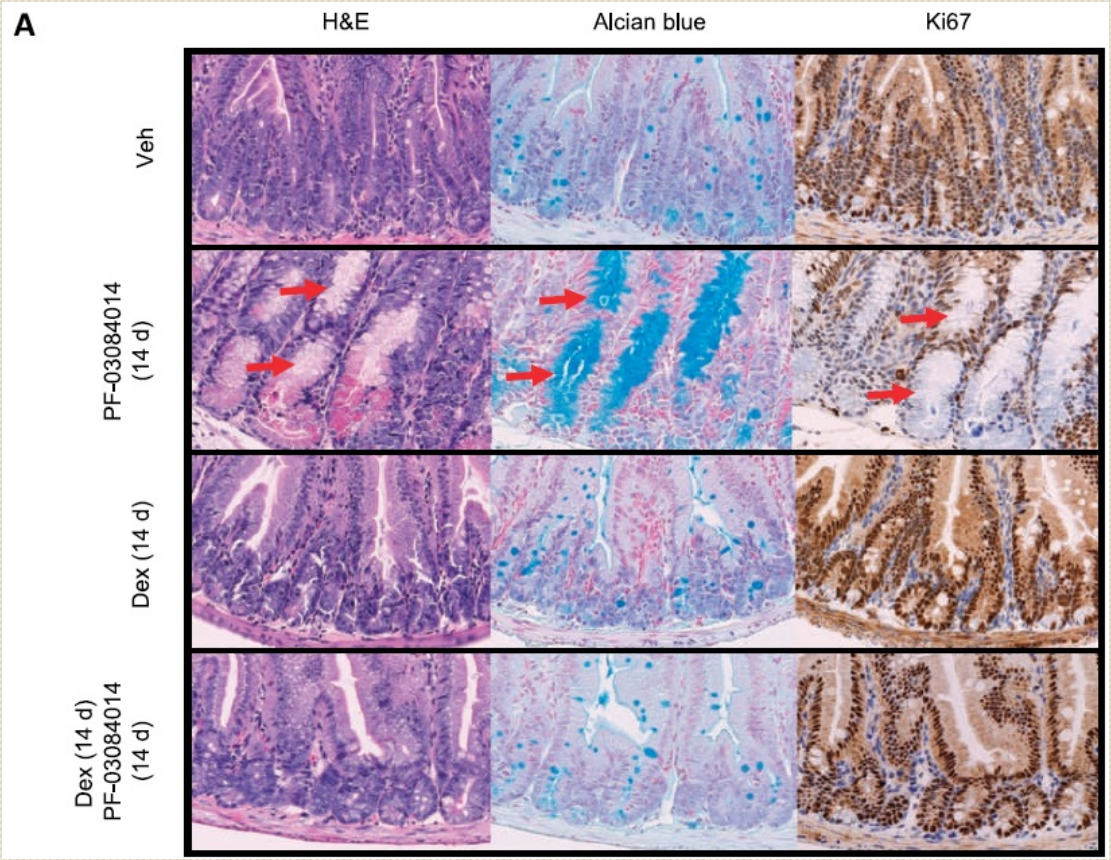
Addapted from: *Cancers* **2011**, *3*, 716-729

Targeting Agents– Clinical Trials Merck



ClinicalTrials.gov
Clin. Cancer Res. **2013**, *19*, 1512-1524
Brit. J. Cancer **2014**, *111*, 1932-1944

Targeting Agents– Combinations



Mol. Cancer Ther. **2010**, *9*, 1618-1628