NON-CONFIDENTIAL SCIENCE OVERVIEW

TASIN

Targeted Anticancer Therapy

April 2019

BARRICADE THERAPEUTICS

BARRICADE THERAPEUTICS

We are developing a first-in-class, oral, small molecule targeting a colorectal cancer (CRC) mutation found in over 80% of ~1.4 million CRC patients. We've already seen unprecedented activity in animal models leveraging **synthetic lethality**, without toxicity. And we have a clear development strategy to reach human proof of concept in 2021.

There are also some very interesting opportunities in de-myelinating diseases — such as multiple sclerosis.

Founded:

2017

Early Stage, Pharmaceutical Company

- Privately held: Dallas-Fort Worth, TX
- Experienced team: long history of collaboration

BARRICADE THERAPEUTICS

TASIN

Lead Program:
Colorectal Cancer

- Potent, **first-in-class** small molecules licensed from University of Texas Southwestern Medical Center
- Selective for **truncated APC**, an important and highly prevalent mutation in and marker of colorectal cancer (CRC)
- **Strong preclinical POC**; currently selecting lead molecule
- Mechanism of Action via **inhibition of EBP**, intermediate enzyme in cholesterol biosynthesis
- Represents a unique and large commercial **opportunity**
- **Human Proof of Concept: 2021**

$7.5MM

Over the next
12 Months

- $1.5MM **convertible note** open to fund TASIN lead selection/neurology animal studies
- $6MM **Series Seed II** 2019 to fund TASIN to IND and advance neuro
- Larger **Series A in 2020** to fund TASIN clinical POC and neurology IND/Phase 1

- **Upside opportunity: demyelinating diseases**
  - Compelling early stage data
  - Large market with significant unmet needs
  - **Potential Human Proof of Concept: 2021**

Barricade Management Team

Neil Thapar, Pharm.D., R.Ph.

- CEO and Chief Scientific Officer
- ReCode, ESSA, Claria Biosciences, Reata, MDACC Pharmaceutical Dev. Center, UTMD Anderson Cancer Center, University of Houston, University of Western Ontario
- 18 years industry experience

John Walling, Ph.D.

- Chief Operating Officer
- Salarius, Reata, ILEX, Cambrex Corp., Abbott Laboratories, Iowa State University
- 31 years industry experience

Melissa Krauth, MBA

- Chief Business Officer
- Reata, Curative Ventures, 2M Biotech, Claria Biosciences, Accenture (clients J&J, AZ, GSK, Millennium), Rice University, The Wharton School
- 25 years industry experience

Scientific Advisory Board

Jef K. De Brabander, Ph.D.

- Department of Biochemistry, UT Southwestern, Dallas, TX
- The De Brabander Lab integrates complex molecule synthesis, medicinal chemistry, molecular pharmacology, and chemical biology to discover and advance novel first-in-class small molecules

Deepak Nijhawan, M.D., Ph.D.

- Department of Hematology/Oncology, UT Southwestern, Dallas, TX
- The Nijhawan Lab focuses on target identification studies of small molecules and drugs

Sunil Sharma, M.D., F.A.C.P., M.B.A.

- Deputy Director, Tgen Clinical Sciences
- Professor and Division Director, Applied Cancer Research & Drug Discovery
- Leading expert in gastrointestinal cancers & oncology drug development.

TASIN

(Truncated APC Selective Inhibitor)

CRC Landscape

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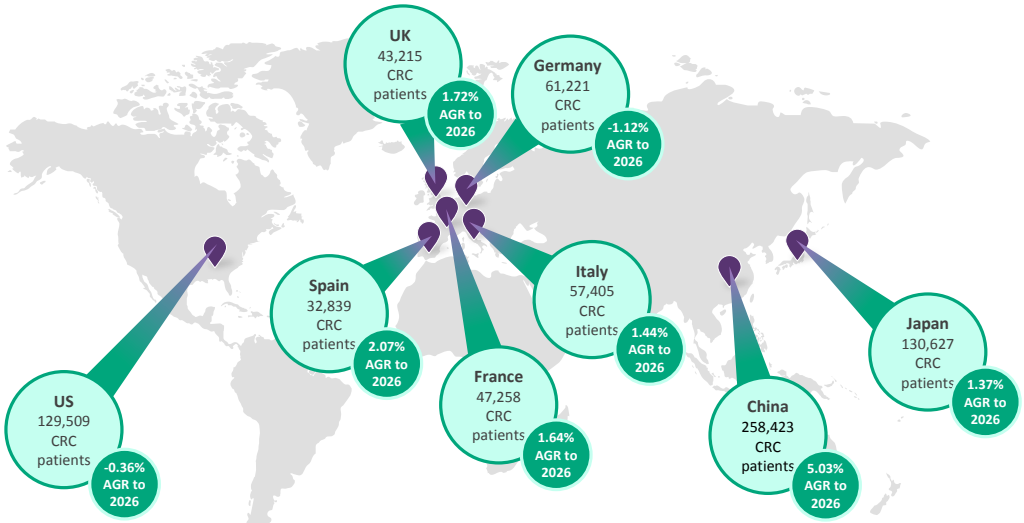
Colorectal cancer (CRC) is the third most common cancer globally, with significant unmet needs.

CRC Incidence (2016)



Declining diagnosed incidence rates in the US and Germany can be attributed to limited population growth and to the population-based screening programs that have been put into place in these markets, which lead to the removal of precancerous polyps from the colon and rectum.

CRC Survival

CRC Stage	Description	5-Yr Survival	
IV	Distant metastases	8.1%	← Barricade Entry Point
III	Nodal involvement	59.5%	↓ Barricade Expansion Opportunities
II	Invasive tumor No nodes No mets	82.5%	

Source: GlobalData Colorectal Cancer: Competitive Landscape to 2026; April 2018

Recent CRC Market Developments

KEYTRUDA® OPDIVO™ + YERVOY®

- PD-1 Inhibitors approved in patients with high microsatellite instability (MSI-H) or mismatch repair deficient (dMMR) (**12-15% of patients**) based on tumor response rate; survival not yet reported.

TECENTRIQ®

- PD-L1 inhibitor: failed CRC trials

~50%

- EGFR inhibitors indicated patients w/wild-type KRAS/BRAF/NRAS

Despite these new options, survival in late-stage disease remains poor, with high need for new treatment options

Source: GlobalData Colorectal Cancer: Competitive Landscape to 2026; April 2018

Truncated APC is the earliest occurring mutation in CRC, affecting the vast majority of CRC patients.

APC

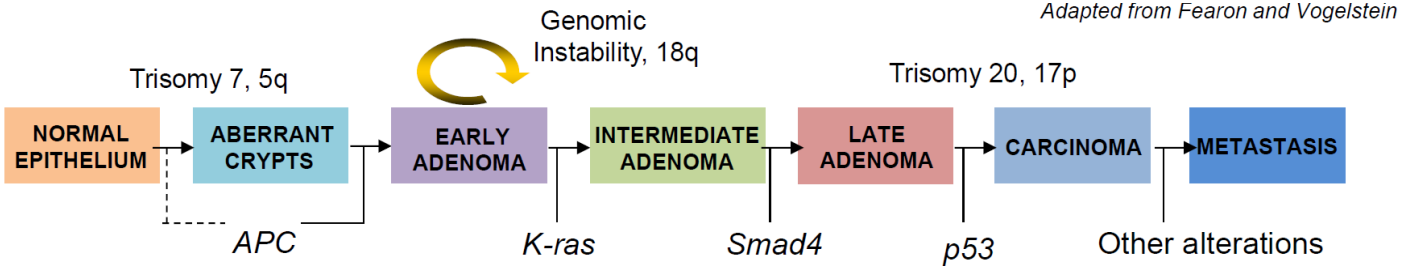
Normal, full-length Adenomatous Polyposis Coli is a tumor suppressor gene.

APC^{trunc}

Mutated or Truncated APC has a dominant role in the initiation and progression of CRC such as familial adenomatous polyposis (FAP)

- APC^{trunc} is also found in breast, pancreatic, and lung cancers[1]

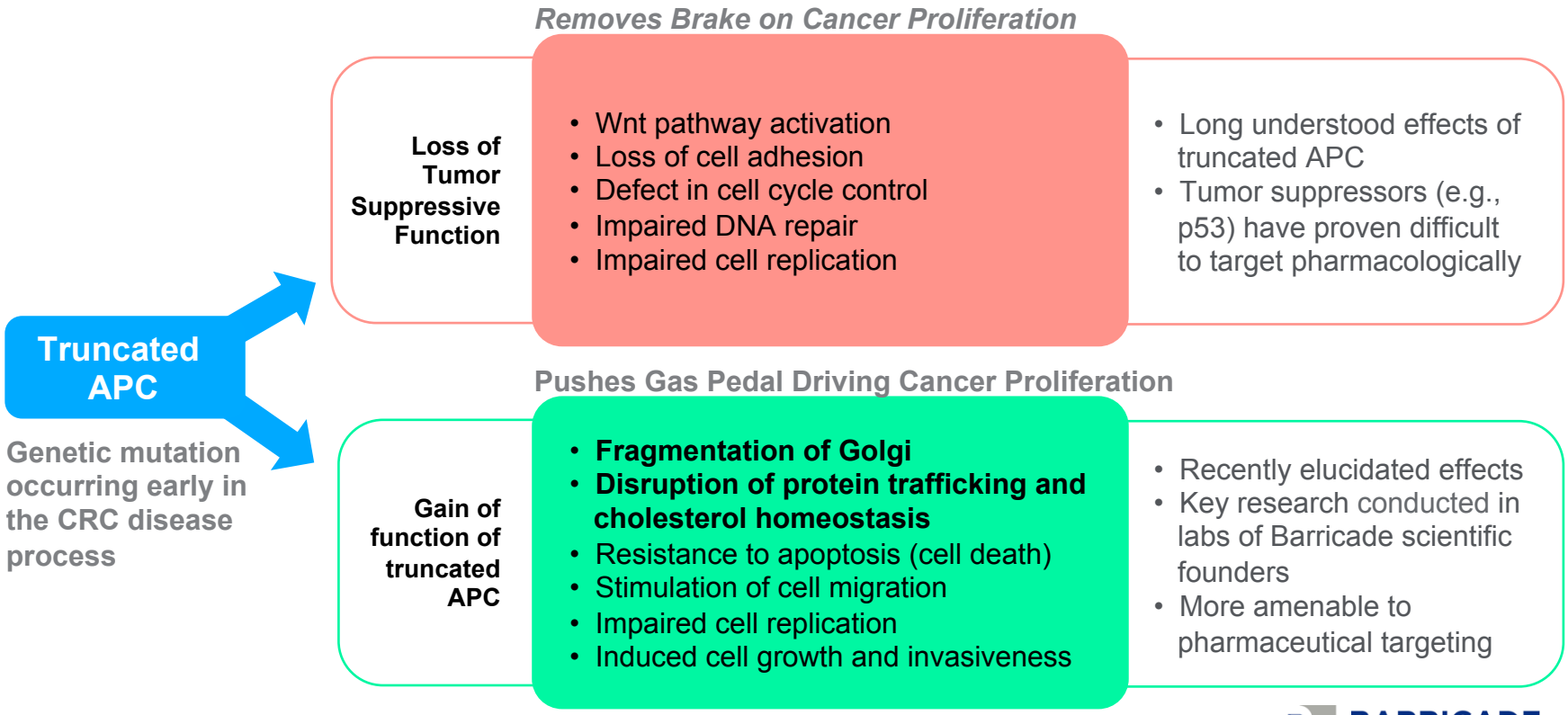
Adapted from Fearon and Vogelstein



- **Clinical Prevalence and Diagnostic**
  - APC^{trunc} is expressed in >80% of CRC tumors
  - APC^{trunc} verified by the FOUNDATIONONE®CDx (Companion Diagnostic)[2]

1. Lesko et al. Exploiting APC Function as a Novel Cancer Therapy. Current Drug Targets. 2014, 15, 90-102.
2. https://www.foundationmedicine.com/genomic-testing/foundation-one-cdx

UTSW scientists helped elucidate how truncated APC leads to cancer, paving the way for new therapies.



Zhang L, Shay J,. Journal Natl Cancer Inst (2017)
BT, data on file, 2018

Barricade is targeting a very large commercial opportunity in metastatic CRC, with major upside in earlier stage disease.

Drug	Peak Sales and US Pricing*	Comments
Avastin **VEGF Inhibitor**	$3.3B $62K (1st line)	1st line metastatic disease + chemo Biosimilars expected 2020
Keytruda **PD-1 inhibotor**	$1.29B >$100K	Metastatic disease Primarily in MSI-I mutation in only 4% of CRC cases
Erbitux **EGFR inhibitor**	$1.19B $97K (1st line)	1st line metastatic disease + chemo Target ~50% of cases with WT KRAS/RAS Patent expired 2018
Vectibix **EGFR Inhibitor**	$705MM $93K (1st line)	Same population as Erbitux Patent expires 2020
Stivarga **Kinase inhibitor**	$244MM $42K (3rd line)	3rd or 4th line metastatic disease High toxicity
Longsurf **Chemotherapy**	$307MM $33K (3rd line)	3rd or 4th line metastatic disease High toxicity

**As estimated by Global Data, through 2025*

- **Large number of patients treated in the US for metastatic colorectal cancer**
  - 28K diagnosed with Stage IV/year
  - ~20K relapsing from earlier stage disease
  - Receive average of 4 lines of treatment
- **Most patients eligible for APC^{trunc} Therapy**
  - 80% with truncated APC mutation
  - Toxicity profile should be favorable, allowing combination with other agents
- **Upside opportunity in earlier stage CRC**
  - Large unmet need to prevent recurrence
  - 35K Stage III patients/year; 93% get chemo
  - 34K Stage II patients/year; 37% get chemo
  - Total APC^{trunc} market potential 36K patients/yr
- **US Pricing has been favorable**
- **CRC: Multi-billion dollar revenue opportunity**

TASINs

(Truncated APC Selective Inhibitors)

TASIN Discovery and Preclinical Proof of Concept

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Barricade's scientific founders discovered TASIN by screening for drugs that selectively kill cancer cells with truncated APC.

200,000 Compound Library

↓

6,703 Compounds > 50% inhibition of APC^{trunc} isogenic cell line

↓

126 Compounds selected with > 50% inhibition in APC^{trunc} cells relative to APC mutant (non-truncated) isogenic cells and normal HCECs

↓

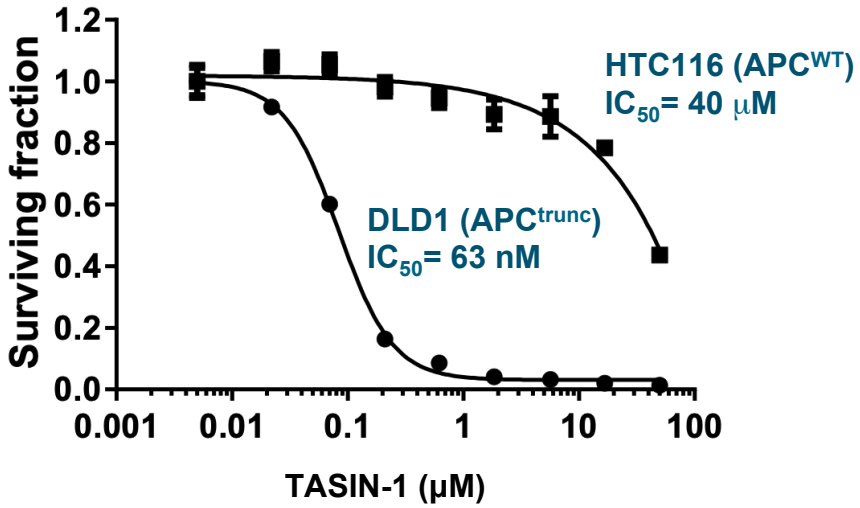
14 Tested top compounds in DLD1 (APC^{trunc}) and HCT116 ($APC^{wild\text{-}type}$)

TASIN-1
63 nM IC_{50} in APC^{trunc} (DLD1)

HCECs; human colonic epithelial cells, BT data on file

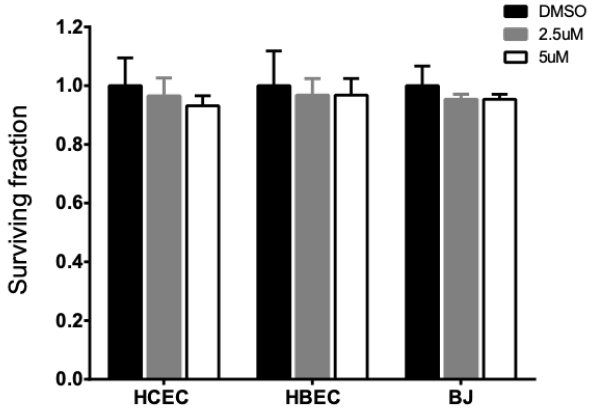
TASIN-1 is highly potent in killing cancer cells with the APC^{trunc} mutation, and relatively non-toxic to cells without the mutation.

Cancer Cell *in vitro* Assay



Across a Panel of >30 cancer cell lines, TASIN-1 demonstrated a similar pattern of selective killing in cells with a truncated APC mutation

Normal Cells *in vitro* Assay



Cell line	TASIN-1 IC_{50} (µM)	APC status
HCEC	>100	WT
HBEC	>100	WT
BJ	>100	WT

TASIN-1 is non toxic in normal cell lines

BT data on file; HCEC = Normal Human colonic epithelial cells; HBEC = Normal Human bronchial epithelial cells; BJ= Normal diploid human fibroblast cells (BJ)

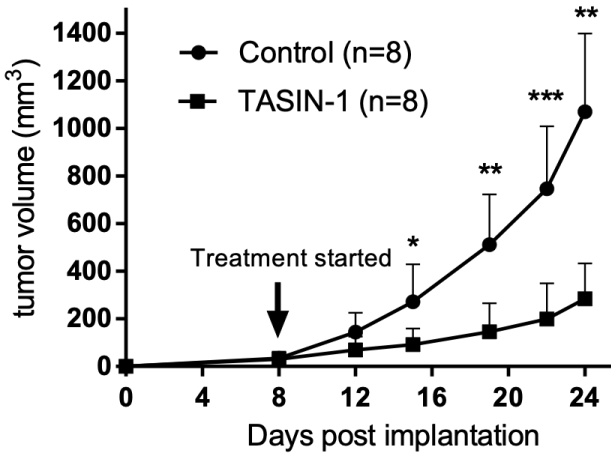
TASIN-1 killed colon cancer cells with the APC^{trunc} mutation in the presence of other common mutations.

Colon Cancer Cell line	HCT116	HCT116 p53-/-	RKO	Lovo	Caco-2	SW480	SW620	HT29	DLD1
IC_{50} (μM)	42	40.8	36.8	7.5	5.2	3.6	3.6	0.075	0.063
Truncated APC Mutation				✓	✓	✓	✓	✓	✓
KRAS Mutation	✓	✓		✓		✓	✓		✓
TP53 Mutation/Null		✓			✓	✓	✓	✓	✓
BRAF Mutation			✓		✓			✓	
PIK3CA Mutation	✓	✓	✓					✓	✓

TASIN-1 demonstrated the same selectivity for the APC^{trunc} mutation when tested in a pilot animal model.

- Pilot study of un-optimized lead (TASIN-1), with un-optimized dosing schedule
- Despite this, efficacy of TASIN-1 was striking in the very difficult to treat DLD-1 model

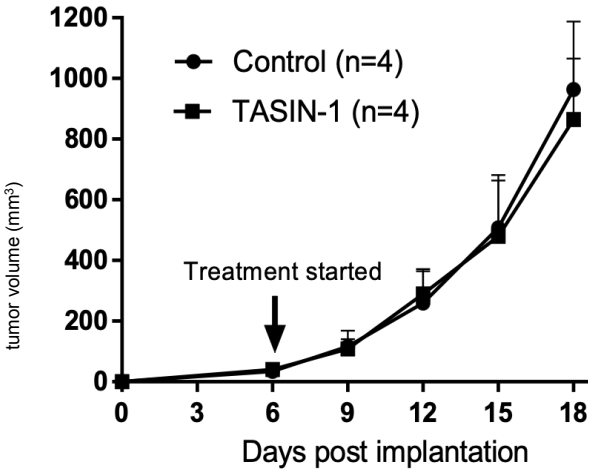
Truncated APC (DLD1 cells)



Tumor growth curves in DLD1 xenograft mice relative to control animals after the 18-day study duration.
* p<0.05; ** p<0.01; *** p<0.001, student's t-test

BT Study Report: TAS-04-01

Wild-Type APC (HCT116 cells)



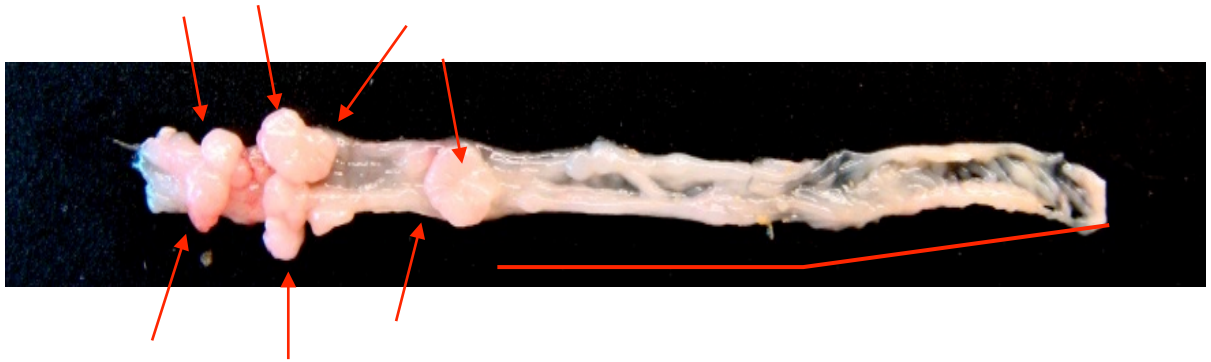
Tumor growth curves in HCT116 xenograft mice relative to control animals after the 18-day study duration.

- **Xenograft mouse model:** Athymic nude mice implanted with tumors from APC^{trunc} cell lines (DLD-1) or APC^{wt} cell lines (HCT-116)
- **Dosing schedule:** 8 days following subcutaneous tumor implantation, animals were administered 40 mg/kg TASIN-1 via intraperitoneal injection (IP), twice daily for 18 days

Similar efficacy was observed in a genetic mouse model of colon cancer.

- **TASIN-1 results in decreased number and size of polyps in the CPC;*Apc* genetic mouse model**

TASIN-1: Healthy translucent colon with a few small pink polyps



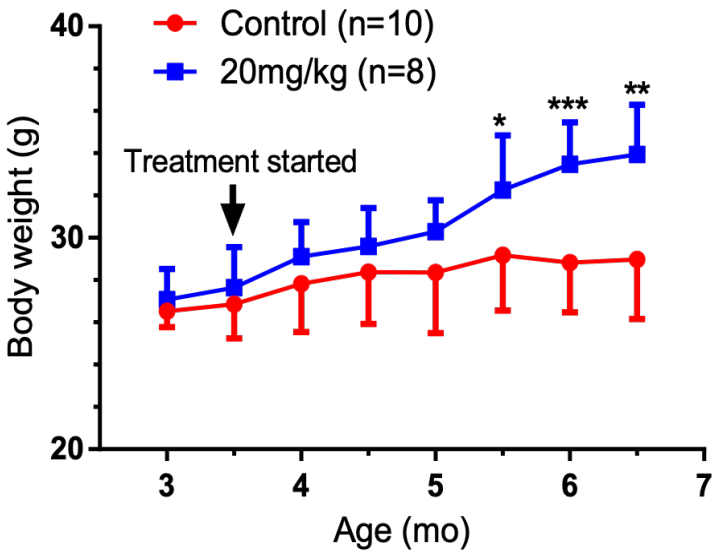
Control: Many large pink polyps (red arrows)

- **Genetic mouse model:** *CPC;Apc* CDX2P-NLS Cre;Apc+/loxP mouse (provided by Dr. Eric Fearon)
  - Have conditional inactivation of APC (expression of APC580) in colon epithelial cells
  - Develop colorectal tumors similar to human
- **Dosing schedule:** ~110 day old mice were injected 20 mg/kg via i.p. twice weekly for 90 days
- **Body weight:** Measured every 15 days

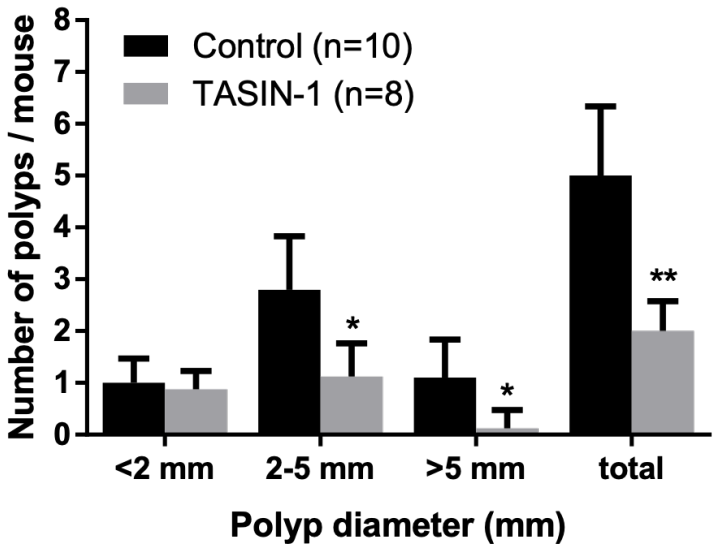
BT Study Report: TAS-04-02

Similar efficacy was observed in a genetic mouse model of colon cancer (cont'd).

- **TASIN-1 treated animals gained weight over the 90-day treatment period**



CPC;Apc mice body weight curves over the 90-day treatment period. TASIN-1 treated animals gained weight over the study duration. Vehicle treated control animals did not gain weight with age.
*, p<0.05; **, p<0.01;***, p<0.001 Student's t-test



*, p<0.05; **, p<0.01 Multiple t-test, FDR=1%

BT Study Report: TAS-04-02

Mechanism of TASIN-induced toxicity in cells with truncated APC

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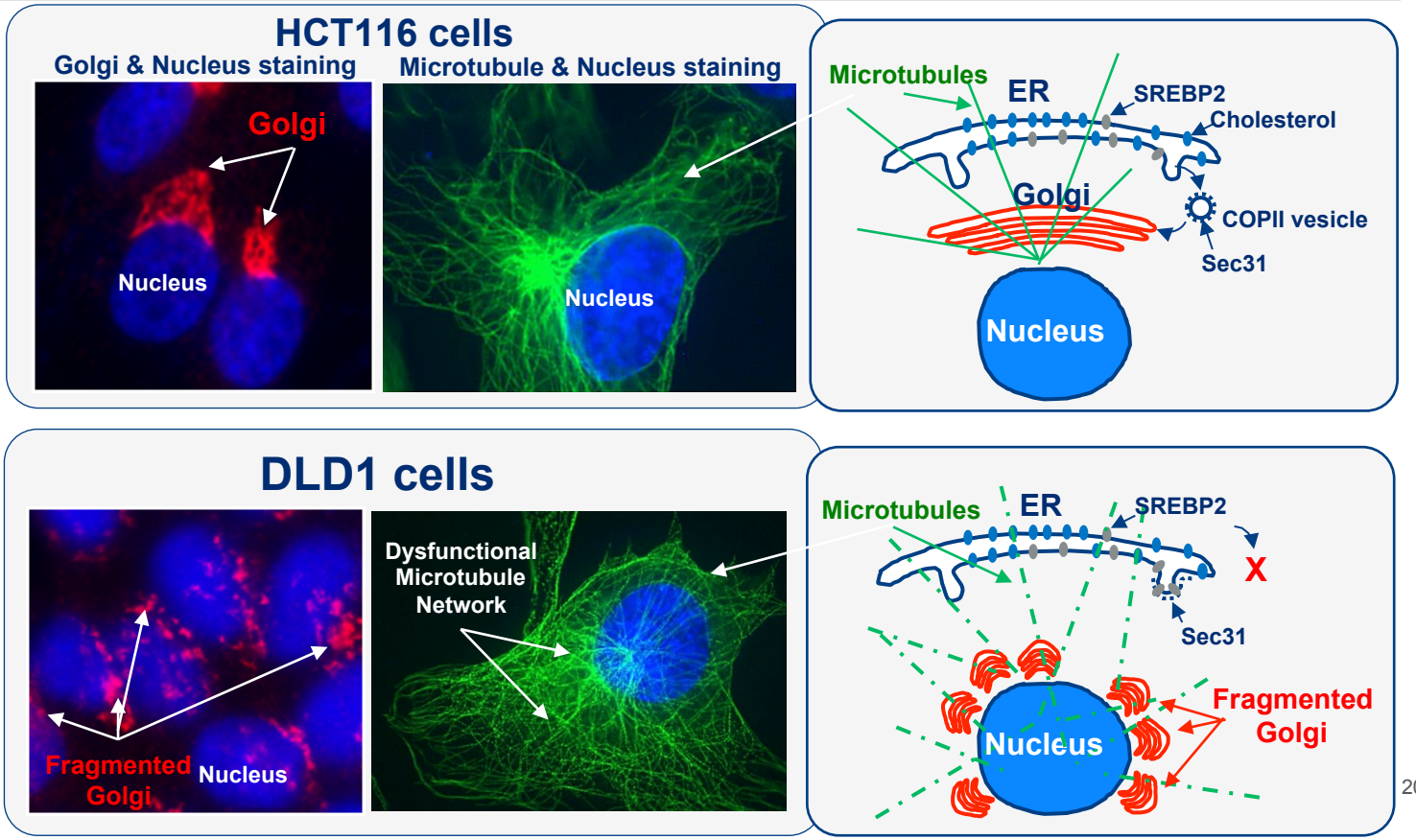
Cells with truncated APC have fragmented Golgi and dysfunctional microtubule network.

APC wild-type

APC truncation

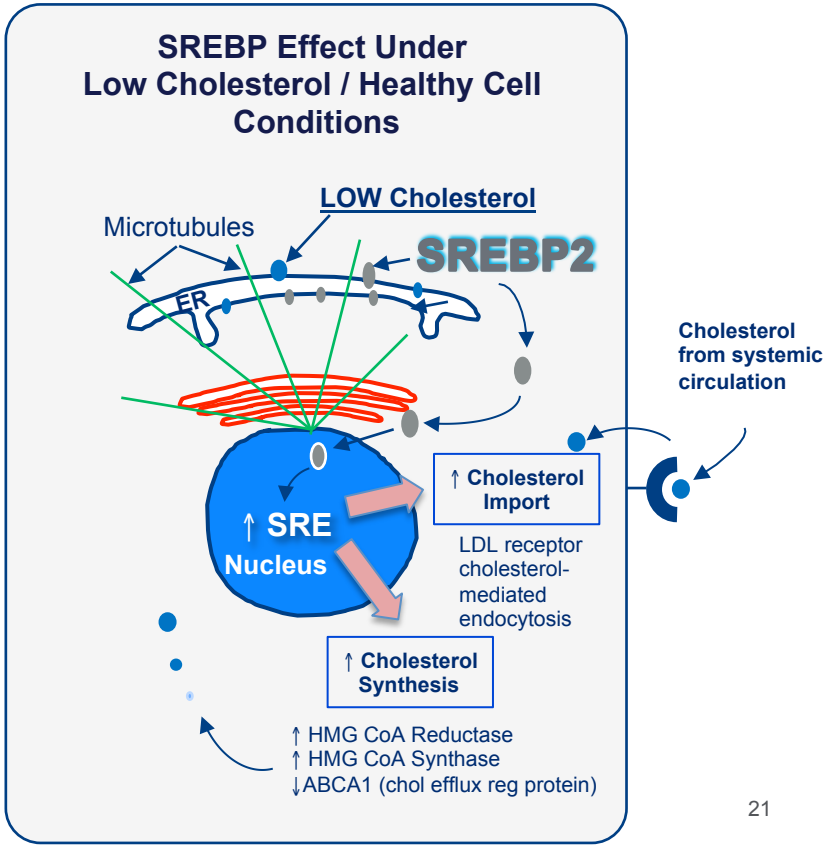


Functional Golgi and microtubule networks allow a healthy cell to effectively synthesize and import cholesterol via SREBP.

Sterol Regulatory Element Binding Protein (SREBP) is a transcription factor which regulates multiple genes involved in cholesterol synthesis and uptake.

Upon sensing of low cholesterol in functional cells:

1. **Cleavage of ER-membrane bound SREBP2 occurs**
2. **The cleaved or "Mature" SREBP translocates to the nucleus via the Golgi**
3. **SREBP enters the nucleus & triggers Sterol Response Element (SRE), which:**
   - ✓ increases cholesterol synthesis
   - ✓ imports extracellular cholesterol

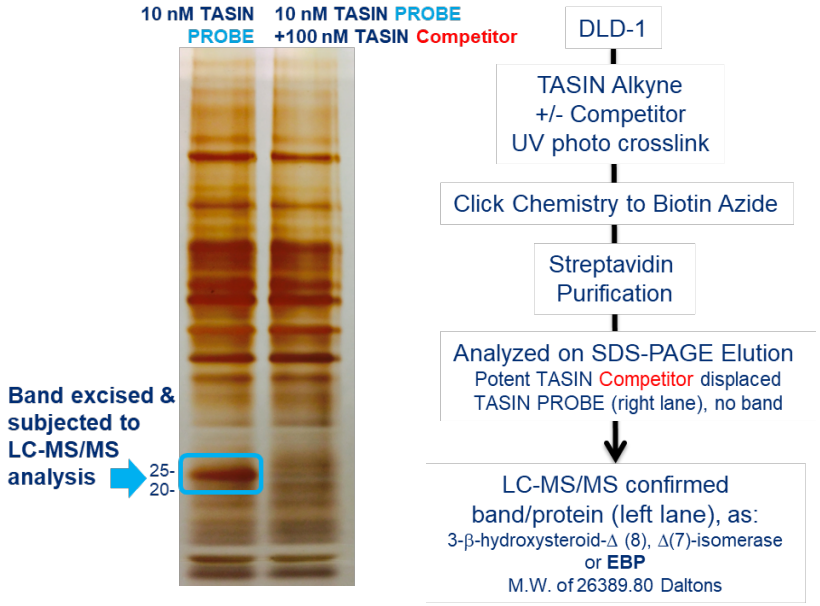


SRE; sterol response element,
SREBP; sterol regulatory element binding protein
Brown, M. S. & Goldstein, J. L. The SREBP pathway: regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor. Cell 89, 331-340 (1997).

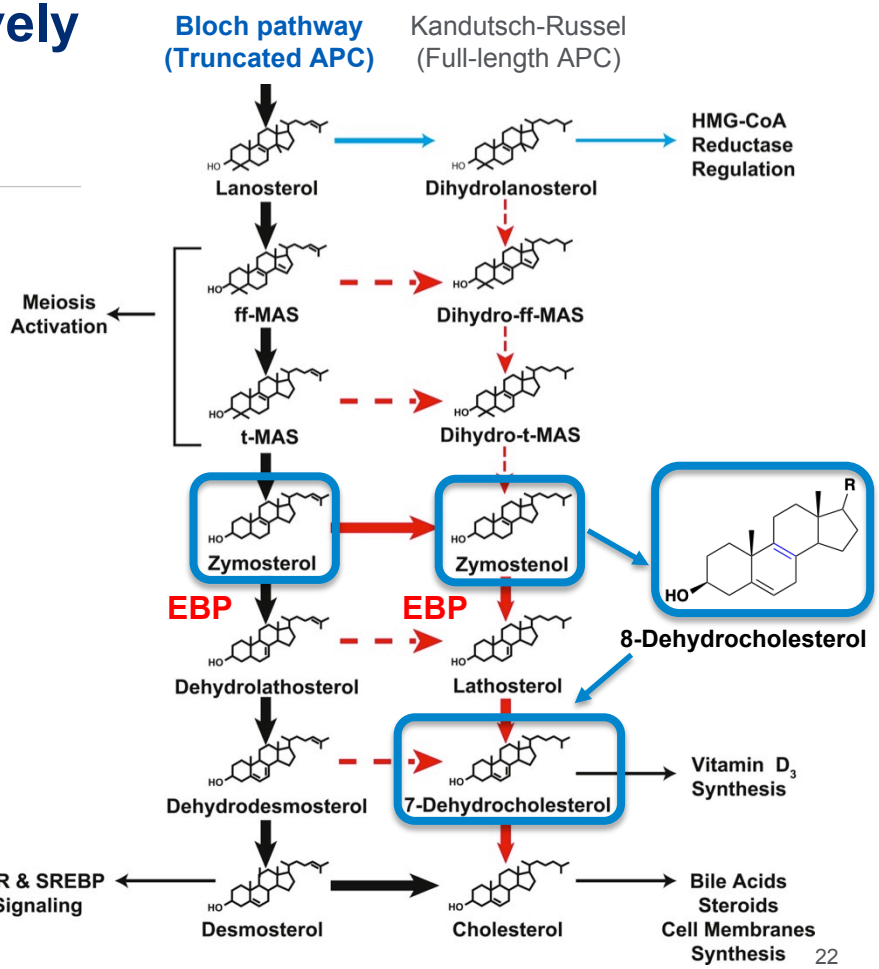
TASINs have been shown conclusively to bind to EBP, a key enzyme in the cholesterol biosynthesis pathway.

TASIN binding to EBP (emopamil-binding protein) confirmed by:

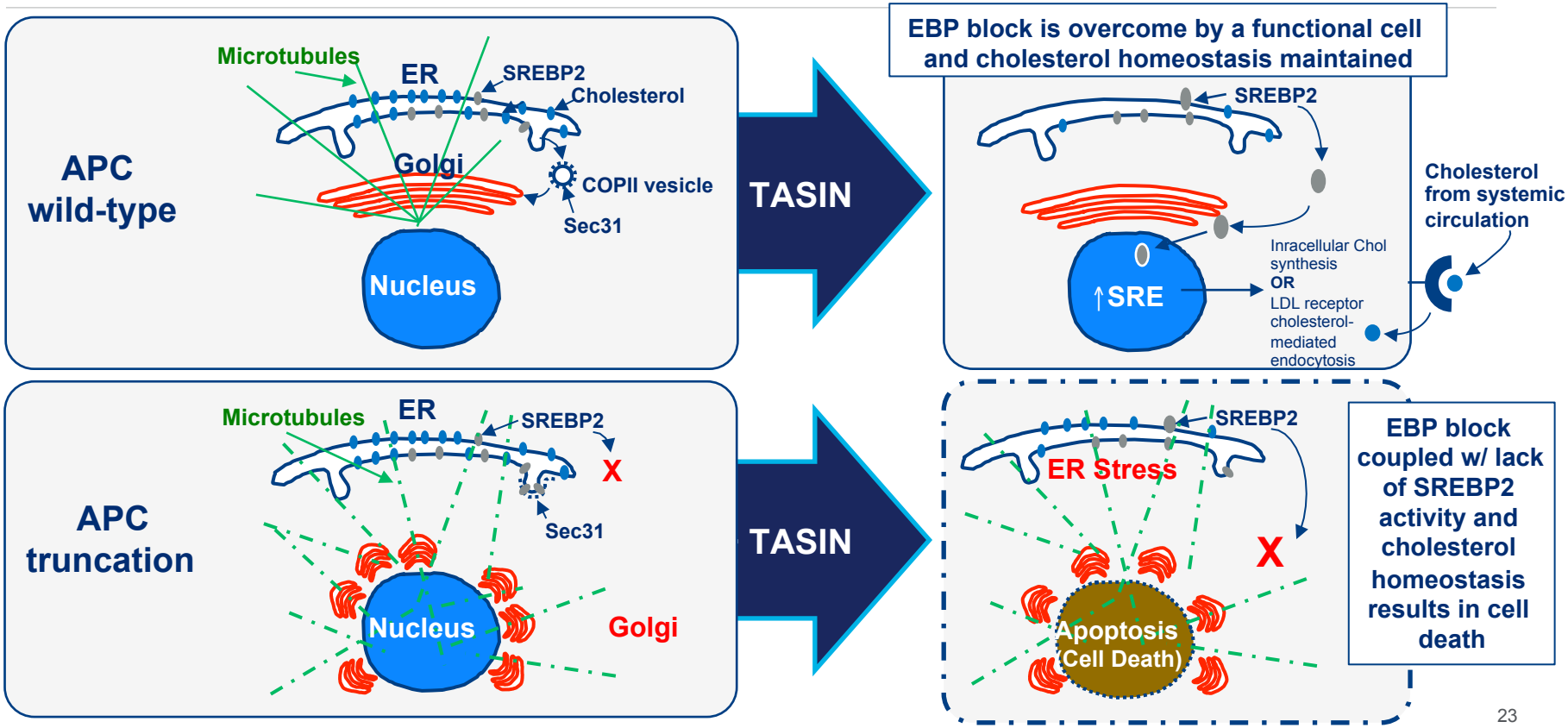
✓ Streptavidin pulldown and LC-MS/MS analysis (below)
✓ CRISPR



BT Study Report: TAS 05-00

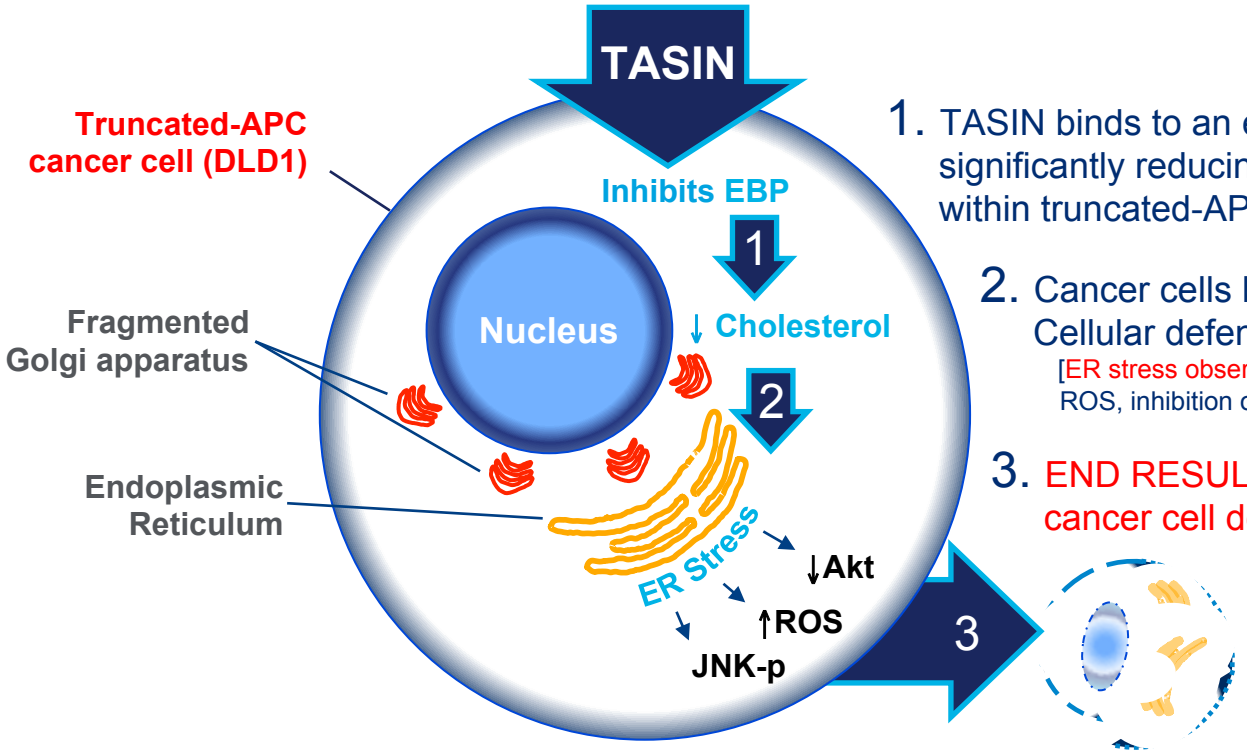


Blocking EBP is a “final insult” in cells with truncated APC that can’t compensate via functional SREBP2 activity.



SRE; sterol response element,
SREBP; sterol regulatory element binding protein

Cytotoxicity Overview: TASIN disrupts intracellular cholesterol, which is critical for truncated-APC cancer cell survival



1. TASIN binds to an enzyme (EBP), significantly reducing cholesterol levels within truncated-APC cancer cells.

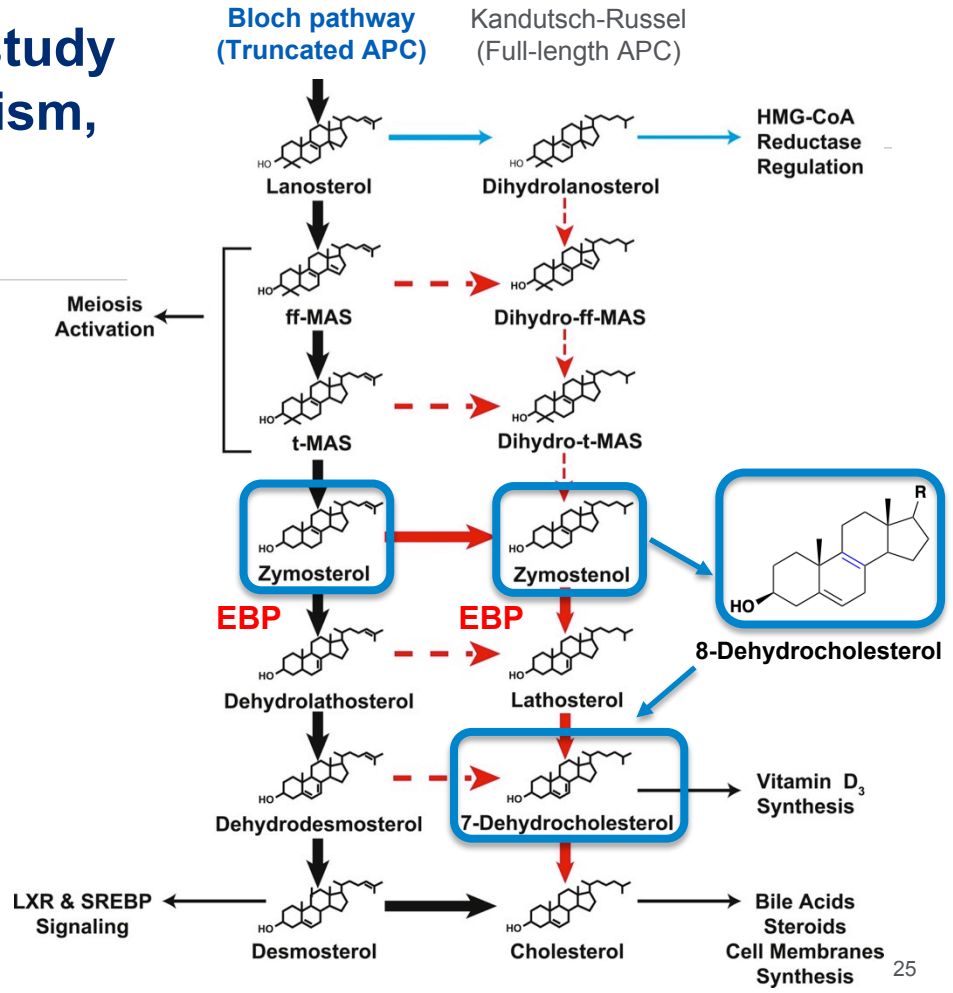
2. Cancer cells become stressed. Cellular defenses are disrupted.
   [ER stress observed: JNK activation, increase in ROS, inhibition of Akt "pro-survival" cell signaling.]

3. END RESULT: colorectal cancer cell death. (apoptosis)

Zhang L, Kim S, Luitel K, Shay J,. Mol. Cancer Ther. (2018)

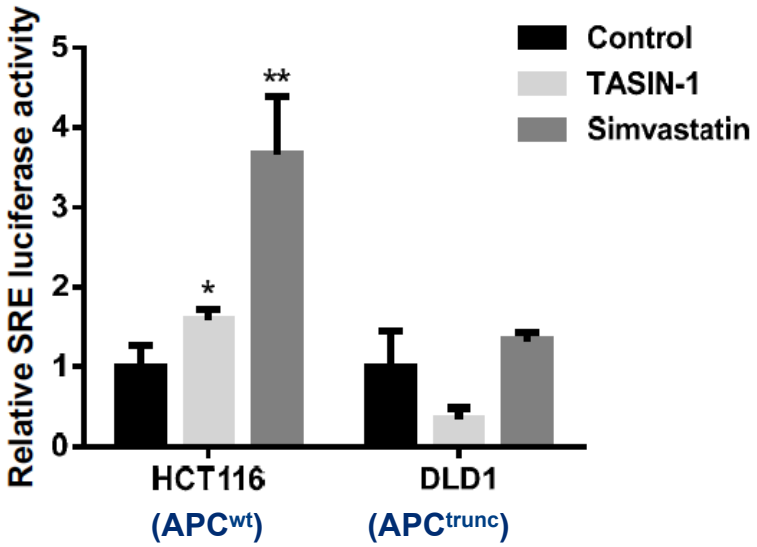
Barricade scientists continue to study additional aspects of the mechanism, in collaboration with leading cholesterol experts.

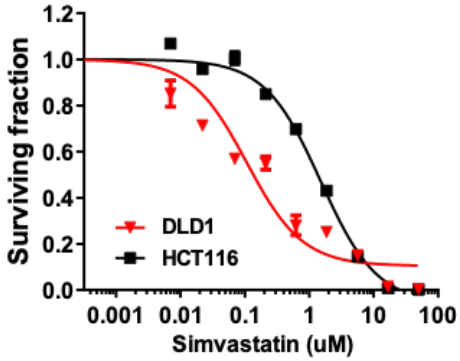
- **Impact of inhibiting other enzymes on the pathway**
  - Data suggests EBP is the only enzyme target that produces the desired results
- **Presence and impact of different cholesterol intermediates**
  - ZymosteRol vs. ZymosteNol/7-DHC/8-DHC
  - How does the ratio of these intermediates change with TASIN treatment in cells with truncated APC vs. wild-type?
  - Do these ratios contribute to cytotoxicity?
  - What are implications for cancers with dysfunctional cholesterol homeostasis (but don't have the truncated APC mutation)?

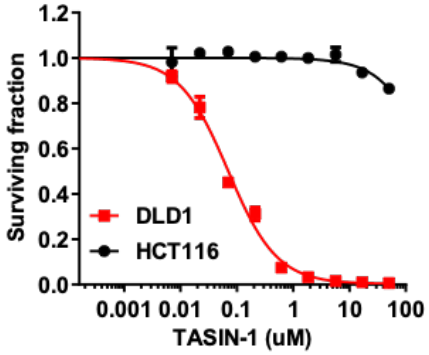


Statins, which target an enzyme upstream of EBP in cholesterol synthesis, do not have the same effects.

- **TASIN was more <u>selective</u> and <u>potent</u> than simvastatin in DLD1 (APC^{trunc}) cell lines**







- Simvastatin increased sterol response element (SRE) activity > 2-fold of TASIN in HCT116 cells
- Simvastatin increased SRE activity in DLD1 cells relative to control and TASIN

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TASIN Development Program to Human Proof-of-Concept (POC)

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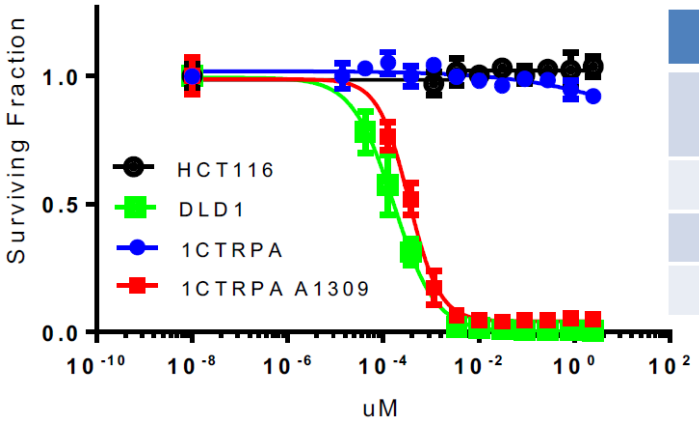
Barricade is exploring several promising TASINs to identify the best compound to move into clinical development.

- >200 TASIN analogs synthesized
- SAR to identify analogs and probes for MOA (EBP binding) experiments



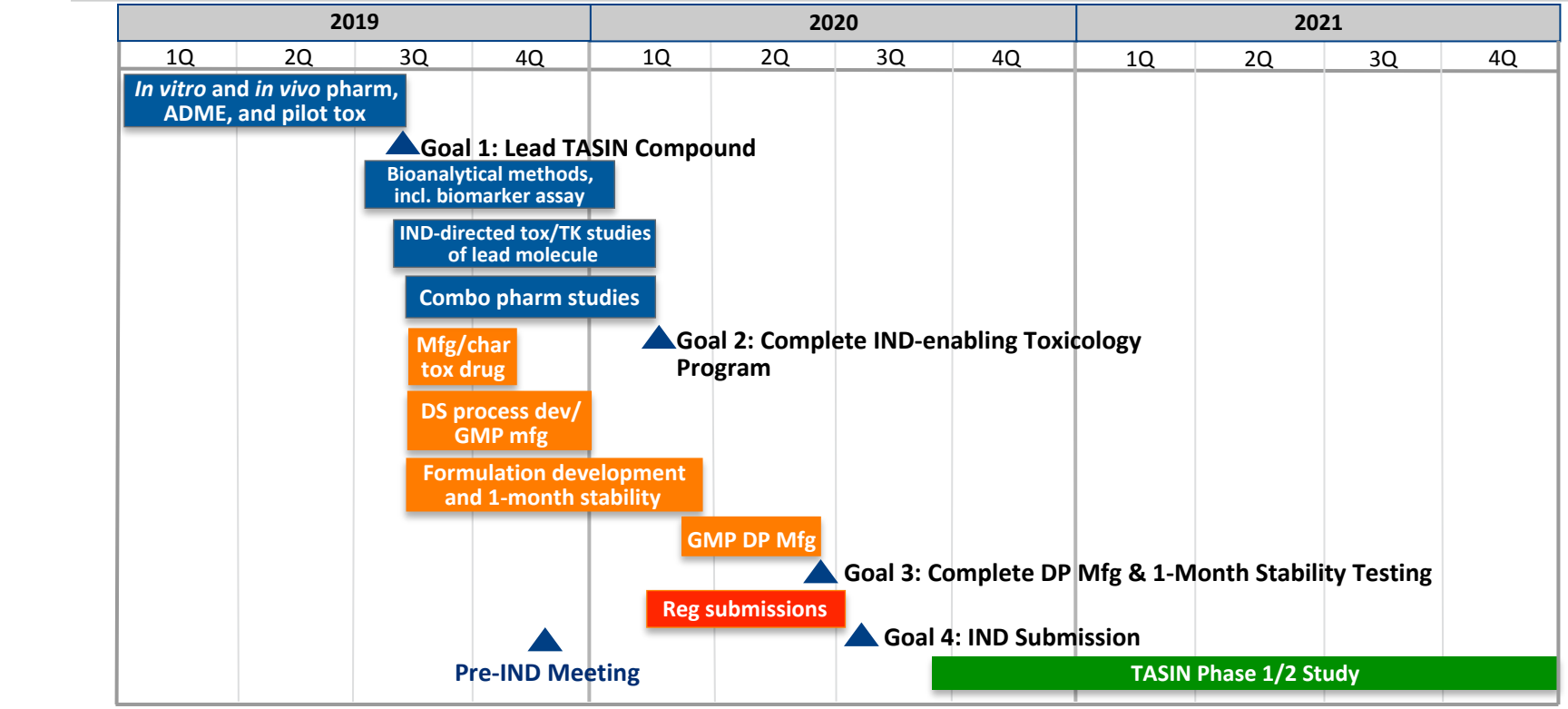
Cell line	IC_{50}
1CTRPA A1309	0.2 nM
DLD1	0.09 nM
1CTRPA	>10 uM
HCT116	>10 uM

	Analog	DLD1 IC_{50} (nM)
Research compound	TASIN-1	63
TASIN analogs for lead selection*	TASIN-2	5
	TASIN-3	38
	TASIN-4	5
	TASIN-5	<1
	TASIN-6	2
	BT-TSN-001	2
	BT-TSN-002	15

*1.5 to >30-fold more potent than TASIN-1

SAR; structure-activity relationship, MOA; mechanism of action,
1CTRPA & HCT116; wild-type APC cell lines
1CTRPA A1309 & DLD1; truncated APC cell lines

Barricade expects to file an IND in 2020, with human proof of concept projected for 2021.



Budget reflects development costs only and excludes personnel, G&A

BARRICADE THERAPEUTICS

Upside Opportunity in Demyelinating Diseases

BARRICADE THERAPEUTICS

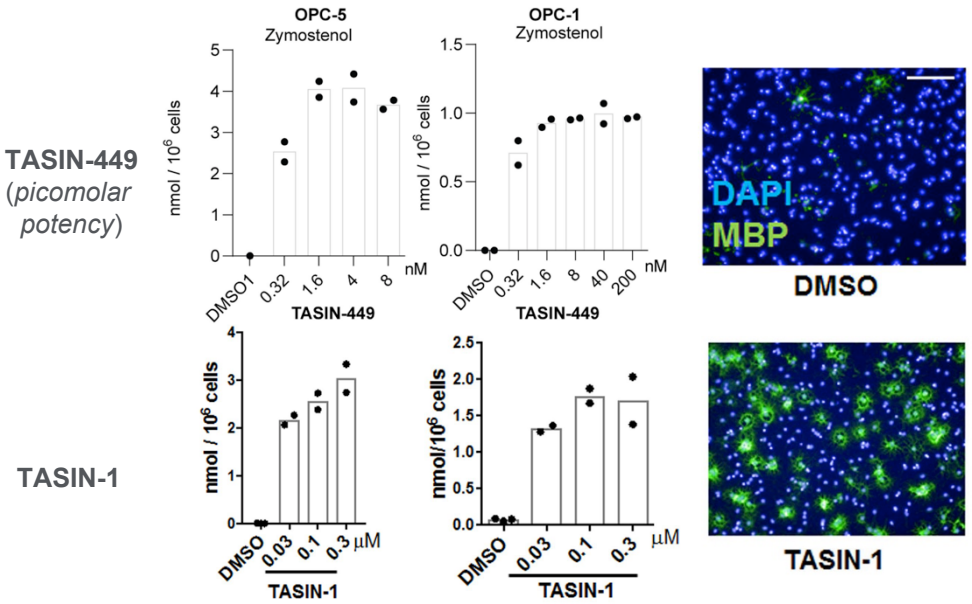
A recently published paper included provocative data suggesting a role for our compounds in neurology.

- **Myelin** is an insulating, fatty sheath that protects nerve cells and speeds conduction of nerve impulses.
- Loss of myelin is the **foundation of many neurological diseases**, including multiple sclerosis.
- Regeneration of myelin is mediated by **oligodendrocyte progenitor cells** (OPCs) which are stem cells in the central nervous system (CNS).
- A recent study at **Case Western** indicated accumulation of select sterol intermediates in the cholesterol biosynthetic pathway promote oligodendrocyte formation.
- TASINs via inhibition of EBP **demonstrated formation** of oligodendrocytes via OPCs (*in vitro*).

Hubler, et al. Nature. Vol 560, 16Aug2018. p372-396.

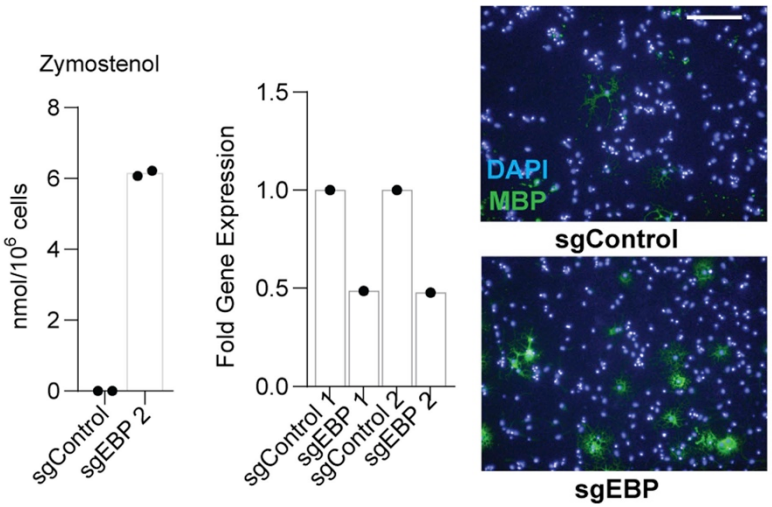
Researchers showed Barricade's TASIN compounds produced myelin via EBP inhibition.

TASINs



Left & Middle: Sterol levels in OPCs treated for 24 h with TASIN-1 or TASIN-449. **Right**: OPC cells treated for 72 h. Nuclei labelled with DAPI (blue), oligodendrocytes (MBP) are indicated by immunostaining (green).

CRISPR/Cas9 – RNA Targeting EBP



Left & Middle: EBP suppression via CRISPR-Cas9 in OPCs with guide RNA targeting emopamil binding protein (EBP). **Right**: OPC cells treated for 72 h. Nuclei labelled with DAPI (blue), oligodendrocytes (MBP) are indicated by immunostaining (green).

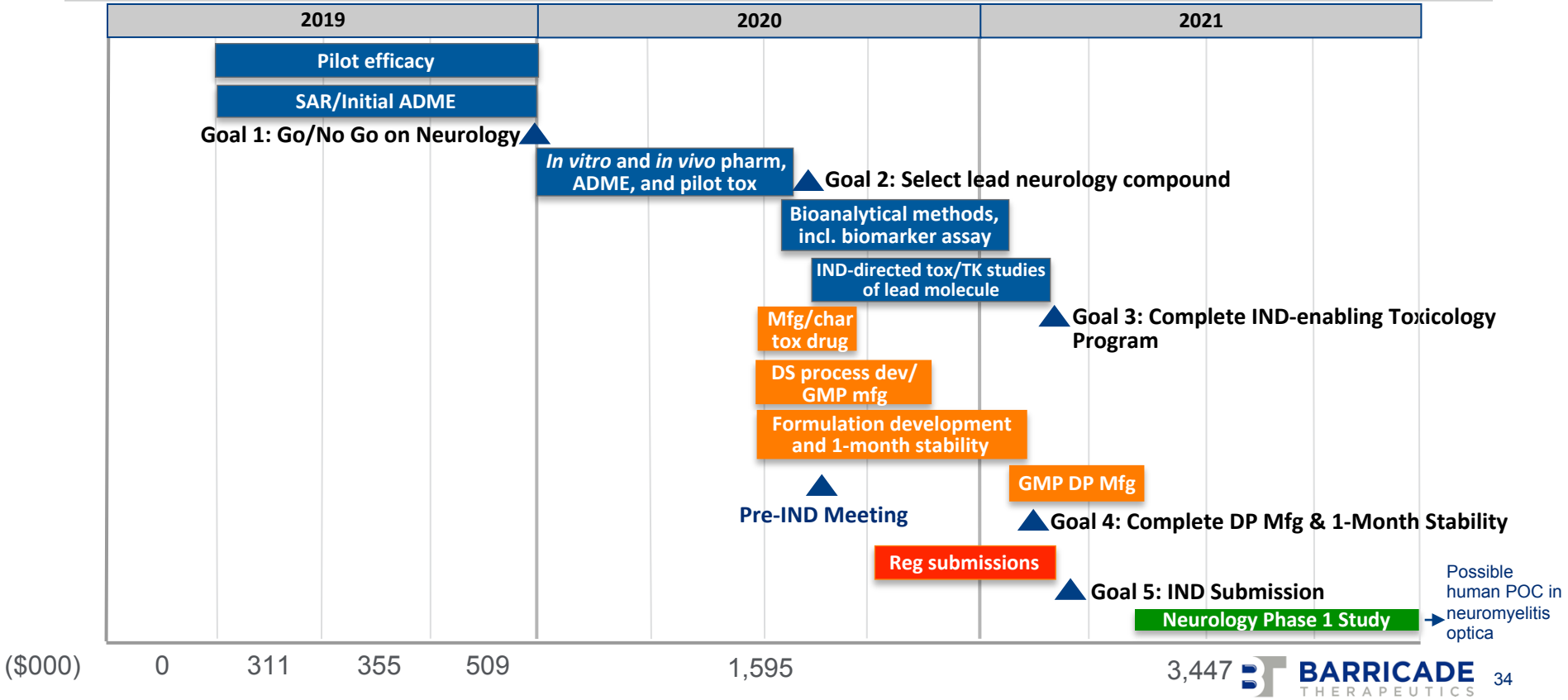
Hubler, et al. Nature. Vol 560, 16Aug2018. p372-396.

MBP+; myelin basic protein-positive

The market opportunity includes the large MS market, as well as a number of orphan diseases.

Disease	Opportunity
Multiple Sclerosis (MS)	Highly prevalent (~1MM US) Multiple successful drugs, but none with remyelinating MOA
Acute Disseminated Encephalomyelitis	Infection-related condition in children; affects 1 in 125,000-250,000 Symptomatic treatments available, but no drug modifying therapy
Balo's Disease	Acute condition that may be fatal; rare rapidly progressing variant of MS Symptomatic treatment with steroids
Charcot-Marie-Tooth Disease	Hereditary condition affecting peripheral nerves (150K in US) Treated with pain medicines and therapy
Guillain-Barre Syndrome	Peripheral nerve condition causing significant weakness (<10K in US) Treated with plasma exchange or IVG
Neuromyelitis Optica	Affects optic nerve; often confused with MS Treated with steroids, plasma exchange, and immunosuppressants
Transverse myelitis	Spinal cord disease affecting 1,400/year, predominantly women Treated with steroids or plasma exchange

The neurology program is approximately one year behind the colorectal cancer program, with potential for POC in 2021 as well.



Budget reflects development costs only and excludes personnel, G&A

Value Proposition & Financing

BARRICADE THERAPEUTICS

TASINs Intellectual Property (IP)

- **Strong global IP position around composition of matter and method of use patents**
  - IP covers all structurally related analogs of TASIN-1 (composition of matter)
  - Recent filing covers new structurally distinct scaffold
  - IP covers EBP targeting (method of use)
  - IP covers use in all therapeutic areas
- **Coverage until 2034 + extensions associated with Hatch Waxman**
- **Additional future IP**
  - Additional structures
  - Formulation or solid-state patents

- **IP is nationalized in the following regions:**
  - United States
  - Europe
  - Canada
  - Mexico
  - Brazil
  - China
  - Hong Kong
  - Japan
  - India
  - South Korea
  - New Zealand
  - Singapore
  - South Africa
  - Australia
  - Russia

TASIN analogs have very favorable manufacturing profile.

- **Reasonable quantities have been readily produced at lab scale with high quality**
  - Small-scale manufacture of the TASINs has been conducted at the University of Texas Southwestern Medical Center (UTSW)
  - Numerous TASIN analogs have been synthesized (2-3 gram quantities)
  - Final compounds structurally verified by $[H]^+$ NMR
  - Purity by HPLC >98%

- **Commercial manufacturing is expected to be straightforward**
  - 2-3 step syntheses from commercially available materials
  - Special synthesis technologies not required
  - Low temperature conditions not required
  - Use of reagents potentially adding genotoxic impurities are not required
  - Anticipate simple oral formulation (capsule)

Barricade is raising $7.5MM to move the CRC program into the clinic and achieve preclinical POC with the neurology program.

	2019	2020	2021
CRC Program	3,069	1,809	1,800
Neurology Program	1,175	1,595	3,447
G&A	797	1,877	2,738
Total	5,041	5,281	7,985
Milestones	CRC lead selection Neuro POC	CRC IND CRC Phase 1 Neuro lead selection	CRC Human POC Neuro Phase 1/potential POC
Proposed Equity Financing	$1.5MM Note $6MM Series Seed II	Series A	
Non-Dilutive Options/ Exit Options	Discovery CRC deal	CPRIT Discovery Neuro deal Preclinical CRC deal	Post-POC CRC deal Preclinical Neuro deal

Discovery deal – business development transaction based on early preclinical data
Preclinical deal – business development transaction based on late preclinical/IND-stage data
Post-POC deal – deal based on human proof of concept data

Summary of TASIN Opportunity

Barricade offers an attractive partnering and investment opportunity with development of a first-in-class drug candidates for lucrative oncology and neurology indications

- **Currently, no Barricade competitor has compounds selective towards APC^{trunc} in development**
- **Strong global IP position around composition of matter and method of use patents, until 2034**
- **Potential TASIN revenue**
  - Total CRC annual U.S. revenue is anticipated > $2.0 BB
  - With a global partner and launches in all major markets, annual WW peak sales are anticipated $6.0BB (assuming U.S. sales are 40% of WW sales)
  - Large upside in neurology indications
- **Pharma partnering options can provide attractive early exit with reasonable investment**
  - CRC partnership
  - Neurology partnership
  - Merger & Acquisition