SYN-020

Oral Intestinal Alkaline Phosphatase
Forward-Looking Statements

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Intestinal Alkaline Phosphatase

A naturally-occurring protein with the unique capacity to treat many diseases

• IAP is a naturally-occurring enzyme produced in the small intestine
  • 150 kD homodimer coordinating Mg$^{2+}$ and Zn$^{2+}$

• Maintains gastrointestinal homeostasis$^1,^2$

• Detoxifies inflammatory mediators$^3$
  • Endotoxin, bacterial DNA, flagellin, nucleotides

• Tightens the gut barrier$^4,^5$
  • Prevents “leaky gut”
  • Diminishes endotoxemia

• Promotes the growth of commensal intestinal flora$^6$

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## IAP has Demonstrated Efficacy in Animals and Humans

<table>
<thead>
<tr>
<th>Model</th>
<th>Outcome</th>
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<tr>
<td><strong>Humans</strong></td>
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<td>Ulcerative Colitis</td>
<td>Clinical improvement in refractory UC at 21 days after 1 week of cIAP nasoduodenal infusion&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>Type 1 Diabetes</td>
<td>T1DM patients had decreased IAP activity in stool; oral IAP supplementation may suppress low-grade intestinal inflammation in T1DM patients&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>Type 2 Diabetes</td>
<td>High IAP levels are associated with protection from T2DM even in obese individuals&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>Ischemic Heart Disease</td>
<td>IAP deficiency is associated with IHD and high IAP levels may be protective against IHD&lt;sup&gt;4&lt;/sup&gt;</td>
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<td>Necrotizing Enterocolitis</td>
<td>High IAP protein levels and low IAP enzyme activity are associated with NEC in infants&lt;sup&gt;5&lt;/sup&gt;</td>
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<td><strong>Mice</strong></td>
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<td>Leaky Gut</td>
<td>Diminished endotoxemia in high-fat diet fed mice&lt;sup&gt;6&lt;/sup&gt;; increased expression of zonulin/occludin&lt;sup&gt;7&lt;/sup&gt;</td>
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<td>Antibiotic-mediated dysbiosis</td>
<td>Accelerated recovery of microbial diversity after antibiotic damage to microbiome&lt;sup&gt;8&lt;/sup&gt; Protected from overgrowth by <em>C. difficile</em> and <em>S. typhimurium</em>&lt;sup&gt;9&lt;/sup&gt;</td>
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<td>Colitis</td>
<td>Improved intestinal tissue histology and inflammatory cytokine profiles in rodent models&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>Metabolic Syndrome</td>
<td>Prevented and reversed multiple symptoms in high-fat diet fed mice&lt;sup&gt;6,11&lt;/sup&gt;</td>
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<tr>
<td>Aging</td>
<td>Decreased age-related inflammation, decreased frailty and extended lifespan&lt;sup&gt;12&lt;/sup&gt;</td>
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Overcoming Key IAP Development Challenges

Synthetic Biologics expertise in protein manufacture and oral delivery

• Manufacturing has limited the clinical progress of oral IAP
  • cIAP is extracted from calf intestine and requires extensive purification, costing up to $10,000/g¹
  • IAP yields are very low (10-500 mg/L) in many manufacturing platforms²⁻⁵

• Synthetic Biologics has developed a stable cell line expressing 2-4 g/L of IAP
  • Synthetic Biologics IAP has equivalent activity to cIAP and is stable in chyme

• Synthetic Biologics has developed oral formulations with different release profiles
  • SYN-020 delayed release capsule formulation proceeding to a Phase 1 clinical trials
  • Patent applications filed around different formulations and release profiles

SYN-020 Prevents Gut Damage from Radiation in Mice

C57Bl/6 mice administered a single dose of whole-body irradiation

SYN-020 prevented shortening of villi and inflammatory infiltrates (left) and preserved endogenous levels of IAP mRNA (Akp3; right) in the intestinal tissue of mice treated with total body irradiation¹

¹Colitis was induced in C57Bl/6 mice (n=5 per group) with total body irradiation at dose of 850 rads. SYN-020 DS (100 U/ml, ~1.5 mg/kg) was added to the cage drinking water from four days prior to radiation until four days after radiation when the animals were sacrificed and tissues collected.
SYN-020 Reduces Radiation-Induced Inflammation in Mice

C57Bl/6 mice administered a single dose of whole-body irradiation

SYN-020 preserved gut barrier function (FITC-Dextran assay; A), maintained expression levels of the tight junction protein zonulin (B) and reduced inflammation (cytokines; C-E) in mice treated with whole-body irradiation¹

¹Colitis was induced in C57Bl/6 mice (n=5 per group) with total body irradiation at dose of 850 rads. SYN-020 DS (100 U/ml, ~1.5 mg/kg) was added to the cage drinking water from four days prior to radiation until four days after radiation when the mice were sacrificed and tissues collected.
SYN-020 Status and Strategy

• Competed IND-enabling GLP Toxicology and Safety Pharmacology Studies
  • Orally-administered SYN-020 was safe and well tolerated at doses up to the highest tested dose of 25 mg/kg/day (NOEL)\(^1\)
  • Excellent delivery of active IAP to the intestinal tract with low-to-no systemic levels
  • IND application submitted to US FDA: Q2 2020

• Initial Clinical Indication
  • Treatment/prevention of radiation enteropathy secondary to cancer therapy
  • Pelvic and abdominal irradiation is used >300,000 times annually in US\(^2\)
  • 60-80% of radiation-treated cancer patients suffer acute bowel toxicity
  • Significant unmet need for both inflammatory acute and fibrosing chronic syndromes

• First clinical trial
  • FDA-requested Phase 1 single ascending dose study in healthy volunteers
  • Toxicology and Phase 1 program will support multiple potential indications

\(^1\)In GLP toxicology studies, SYN-020 oral capsules (dogs) or SYN-020 drug substance (gavage to mice) were administered twice daily for 6-weeks with a 14-Day recovery period. \(^2\)Radiation is used in 50% of cancer patients and has a role in 25% of cures. DS GMP drug substance. DP GMP drug product (encapsulated enteric coated pellets)
SYN-020 (oral IAP)

Additional Slides
Synthetic Biologics Recombinant bIAP II

Equivalent activity to commercial cIAP and stable in chyme

Assay | Sigma cIAP | SYN BIAP II
---|---|---
Specific Activity (U/mg) | 7,000 | 10,000
Activity vs Endotoxin (mU/30min) | 82 | 94

¹Bovine IAP II (BIAP II) is the most potent IAP isoform described to date
SYN-020 Protects the Intestinal Mucosa in Mice

Reduced submucosal inflammation in DSS-colitis model

Male C57Bl/6 mice were treated with Dextran Sulfate Sodium Salt (DSS; 3%) each day for 5 days. SYN bIAP II (100 and 500 U q.d.; n=12 per group) was administered by gavage from days 5-16. Mice were sacrificed on day 17 and tissues collected for histological analysis¹,²

¹Model based on Bol-Schoenmakers M (2010) Eur J Pharmacol. 633:71-7. ²SYN bIAPII is the active drug substance used in the SYN-020 oral formulation; SYN-020 enteric coated pellets are too large to be administered to mice. Efficacy equivalent to literature reports was seen at a SYN bIAP II dose of 100 U/day.
Evaluation of SYN-020 in Radiotherapy

Murine ectopic colon cancer model (BALB/c mice)

| Group 1 (14) | Vehicle oral gavage 0.1 mL BID alone |
| Group 2 (14) | SYN BIAPII oral gavage 100U BID alone |
| Group 5 (14) | Targeted Radiation 10 Gy<br>Vehicle oral gavage 0.1 mL BID |
| Group 6 (14) | Targeted Radiation 10 Gy<br>SYN BIAPII oral gavage 100U BID |

¹Gavage vehicle is 10 mM Tris buffer (pH 7.5) containing 0.1 mM ZnSO4 and 1mM MgCl2. ²SYN BIAPII is the active drug substance used in the SYN-020 oral formulation; SYN-020 enteric coated pellets are too large to be administered to mice. ³After day 15, mice were euthanized if tumor volume >2,500 mm³, tumor was ulcerated, or body weight or overall condition reached animal welfare thresholds.

1Gavage vehicle is 10 mM Tris buffer (pH 7.5) containing 0.1 mM ZnSO4 and 1mM MgCl2. 2SYN BIAPII is the active drug substance used in the SYN-020 oral formulation; SYN-020 enteric coated pellets are too large to be administered to mice. 3After day 15, mice were euthanized if tumor volume >2,500 mm³, tumor was ulcerated, or body weight or overall condition reached animal welfare thresholds.
SYN-020 Does not Interfere with Radiation Efficacy in Mice

1 SYN BIAPII is the active drug substance used in the SYN-020 oral formulation; SYN-020 enteric coated pellets are too large to be administered to mice.

2 Tumor volume measured 3-times per week by digital caliper. Mice were euthanized if tumor volume >2,500 mm³, tumor was ulcerated, or body weight or overall condition reached animal welfare thresholds. RT = radiation treatment targeted to the tumor.
Evaluation of SYN-020 in Colon Cancer

Murine ectopic colon cancer model (BALB/c mice)

CT-26 colon cancer cells

Group 1 (30)
Vehicle oral gavage 0.1 mL BID alone

Group 2 (30)
SYN BIAPII oral gavage 100U BID alone

Group 3 (30)
5-FU i.p. QD
Vehicle oral gavage 0.1 mL BID

Group 4 (30)
5-FU i.p. QD
SYN BIAPII oral gavage 100U BID

15-FU dose 30 mg/kg QD. 2Gavage vehicle is 10 mM Tris buffer (pH 7.5) containing 0.1 mM ZnSO4 and 1mM MgCl2. 3SYN BIAPII is the active drug substance used in the SYN-020 oral formulation; SYN-020 enteric coated pellets are too large to be administered to mice. 4After day 6, mice were euthanized if tumor volume >2,500 mm³, tumor was ulcerated, or body weight or overall condition reached animal welfare thresholds.
Administration of 5-fluorouracil (5-FU) reduced tumor growth (B) and caused diarrhea (A) in the mouse ectopic colon cancer model. Co-administration of oral SYN-BIAPII ameliorated diarrhea without altering 5-FU antitumor efficacy.

1 SYN BIAPII is the active drug substance used in the SYN-020 oral formulation; SYN-020 enteric coated pellets are too large to be administered to mice.
2 Stool consistency score reported as 0 (normal), 2 (loose, formed stools), or 4 (diarrhea)