GMP RESEARCH SUMMARY

Discovering GMP was good, but not good enough.
Over 10 years of pre-clinical and clinical studies led to the purposeful design of **Glytactin** (GMP).
And the ***Glytactin*** *proof continues to grow.*

The research data using Glycomacropeptide (GMP) based Medical Foods for PKU is mounting. GMP is a naturally occurring, whole protein, produced during the cheese making process. It is one of several proteins that make up whey and is the only naturally occurring protein that does not contain Phenylalanine (Phe) in its pure form. GMP must be supplemented with limiting amino acids (AA) to provide a nutritionally complete protein. The 5 limiting amino acids include, Arginine, Histidine, Leucine, Tryptophan, and Tyrosine (Tyr).

Research utilizing GMP protein for PKU began in 2000. Below you will find summaries of vital publications from 3 different research groups in 3 different countries with a total of 78 subjects aged 5 to 49 years old. Three of these studies utilized Cambrooke's patented blend of GMP + limiting AA, called **Glytactin**™, but were not funded by Cambrooke Therapeutics.

Citation	Design	Subjects	Method	% PE & mg Phe/day from GMP	Phe from Diet NOT reduced	Phe Levels Stable	Tyr Levels Stable or Improved	Body Composition Stable	Other Findings or Conclusions by the Authors
MacLeod, EL. et.al. Breakfast with glycomacropeptide compared with amino acids suppresses plasma ghrelin levels in individuals with phenylketonuria. Am J Clin Nutr 2009;89:1068–77 DOI: 10.1016/j.ymgme.2010.04.003	**Prospective, Inpatient Observational Study** Duration of study: Two treatment stages each lasting 4 days with a 2 day wash out prior to starting the trial Phe tolerance verified by one or more 5 day validation periods	11 adolescents and adults in the US Age: 11-31 years Gender: 4 Females 7 Males Classical PKU (n= 10) Variant PKU (n= 1)	• Participants consumed the same low-Phe weighted diet for 4 days with AA-MF followed by 4 days with an experimental GMP-MF • Plasma concentrations of AAs, insulin and ghrelin were drawn fasting and 180 minutes following the start of breakfast • Satiety was assessed using a visual analog scale before, immediately after, and 180 minutes after breakfast	100% PE from GMP for 4 days Daily Phe allowance Mean 13± 2 mg/kg/day Range: 372 mg/day (5.8 mg/kg) up to 1793 mg/day (26.7 mg/kg)	Low-Phe weighted diet was adjusted to maintain the same intake of Phe in each stage of the study	☑	☑	n/a	• The nutritional management of PKU is in need of new dietary options besides synthetic AAs in order to improve metabolic control and control hunger • Results confirm the importance of protein consumption in a meal to improve satiety • Novel evidence that a breakfast containing a GMP-MF suppresses plasma levels of the satiety hormone ghrelin for a longer period of time compared with a breakfast using AA-MF • Medical food products made with the intact, low-phe protein GMP are a first step to providing a more physiologically complete diet that improves dietary options, and facilitates protein distribution with metabolic control of PKU
van Calcar, SC. et. al. Improved nutritional management of phenylketonuria by using a diet containing glycomacropeptide compared with amino acids. Am J Clin Nutr. 2010 Apr;91(4):1072 DOI: 10.3945/ajcn.2008.27280	**Prospective, Inpatient Observational Study** Duration of study: Two treatment stages each lasting 4 days with a 2 day wash out prior to starting the trial Phe tolerance verified by one or more 5 day validation periods	11 adolescents and adults in the US Age: 11-31 years Gender: 4 Females 7 Males Classical PKU (n= 10) Variant PKU (n= 1)	• Participants consumed the same low-Phe weighted diet for 4 days with AA-MF followed by 4 days with an experimental GMP-MF • Compared plasma concentrations of AAs, blood chemistries, and insulin were measured pre and post prandial after AA (day 4) and GMP diets (day 8)	100% PE from GMP for 4 days Daily Phe allowance Mean 13± 2 mg/kg/day Range: 372 mg/day (5.8 mg/kg) up to 1793 mg/day (26.7 mg/kg)	Low-Phe weighted diet was adjusted to maintain the same intake of Phe in each stage of the study	☑	☑	n/a	• GMP, when supplemented properly with limiting AAs, is a safe and highly acceptable alternative to synthetic AAs as the primary protein source in the nutritional management of PKU • As an intact protein source, GMP-MF improves protein retention and phenylalanine utilization based on lower serum BUN, higher plasma insulin levels, and higher plasma AA concentrations when compared with AA-MFs

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CAMBROOKE THERAPEUTICS™

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Ney, DM. et. al. Glycomacropeptide for nutritional management of phenylketonuria: a randomized, controlled, crossover trial. AJCN. 2016 DOI: 10.3945/ajcn.116.135293	**Prospective Randomized Crossover Interventional Study** Duration of study: 3 weeks per stage with 3 week wash out period	30 adolescents and adults in the US Age: 15 to 49 years Gender: 18 Females 12 Males Classical PKU (n= 20) Variant PKU (n= 10)	• Participants consumed a low-Phe diet with AA-MF or **Glytactin** • Obtained plasma AA with Phe & Tyr levels on filter paper • Diet records analyzed for protein, calorie, & micronutrient intakes • Average daily PE intake 80 ±4 g/day	100% PE from **Glytactin** 88 ±6 mg Phe/day from **Glytactin**	☑	☑	☑	☑	• Serum Tyr levels improved with **Glytactin** despite a reduction in intake • Frequency of medical food intake was higher with **Glytactin** GMP-MF (3.74) vs. AA-MF (2.43) • Subjects rated **Glytactin** GMP-MFs as more acceptable (4.47) than AA-MFs (3.34) • GI distress and hunger resolved with **Glytactin** GMP-MF
Pinto, A. et al. Nutritional status in patients with phenylketonuria using glycomacropeptide as their major protein source. Eur J Clin Nutr. 2017 DOI: 10.1038/ejcn.2017.38	**Retrospective Longitudinal Chart Review** Duration of study: 7-13 months on **Glytactin** GMP MF	11 adolescents and adults in Portugal Age: 13 to 42 years Gender: 8 females 3 males Classical PKU (n=6) Variant PKU (n=5)	• Blood Phe and Tyr were analyzed before and after introduction of **Glytactin** • Diet records analyzed for protein, calorie, & micronutrient intakes • Average daily PE intake 80 g/day	Mean 57% of PE from **Glytactin** (27-100%) 34 ±12 mg Phe/day from **Glytactin**	☑	☑	☑	☑	• Serum Tyr levels improved with **Glytactin** despite a reduction in intake • Despite the higher calories from **Glytactin** GMP-MF used, overall caloric intake was decreased possibly related to report of improved satiety • Improved serum Phe/Tyr ratio, which may indicate better executive function, inhibitory control, and reflect serotonin levels in the brain
Daly A. et al. Does the additional phenylalanine in GMP-AA protein substitute lead to destabilization of blood phenylalanine concentrations compared to conventional amino acid protein substitutes? ICIEM. Sept 2017. Abstract 166.	**Prospective, Longitudinal, Interventional Study** Duration of Study: 12 to 24 months	36 children in the UK Age: 5-16 years Gender: 21 boys 15 girls	• 25 received a *GMP based MF (GMP-AA)* and 11 received standard AA-MF • Median PE intake per day = 60 g PE/day (Range 50-80 g PE/day) • Serum Phe levels checked weekly	Mean 73% of PE from GMP Range (33-100%) Median 81 mg Phe/day from GMP-AA	☑	☑	☑	Not Reported	• No significant difference for serum Phe or Tyr levels when 75% of daily PE intake provided by GMP-AA based medical foods • No dietary adjustments need to be made to compensate for Phe provided by GMP-AA based medical foods
Pinto, A. et al. Dietary management of maternal phenylketonuria with glycomacropepetide and amino acids supplements: a case report. Mol Genet Metab Rep. 2017 DOI: 10.1016/j.ymgmr.2017.10.004	**Retrospective Case Report** Duration of Study: 28 months	31 year old G1P0 female with classical PKU and history of poor metabolic control	• **Glytactin** GMP-MF was started to provide 30 PE/day 18 months prior to pregnancy • Total PE from MF increased from 58 to 86 g/day during pregnancy but AA-MF provided all additional PE intake • Serum Phe and Tyr levels checked weekly	35-52% PE from **Glytactin** 46 mg Phe/ day from **Glytactin**	☑	☑	☑	Normal rate of maternal weight gain for pregnancy	• First case reporting the use of **Glytactin** GMP-MF in MPKU • Median blood PHE was 258 µmol/L throughout pregnancy • Serum Tyr levels improved during pregnancy • Some intrauterine development delay occurred in the last trimester, although this was not associated with MPKU syndrome or the use of **Glytactin** GMP-MF